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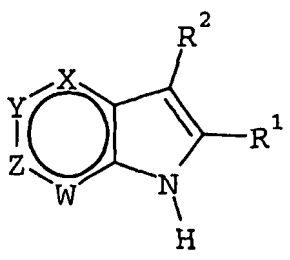
(54) Title: SYNTHESIS OF HETEROCYCLIC COMPOUNDS EMPLOYING MICROWAVE TECHNOLOGY

(57) Abstract: This invention provides for processes for preparing compounds of the formula (I) comprising employing microwave energy.



(I)

SYNTHESIS OF HETEROCYCLIC COMPOUNDS EMPLOYING MICROWAVE TECHNOLOGY

This application is entitled to the benefit of earlier filed applications U.S. 60/300,733, filed June 25, 2001, and GB 0119307.7, filed August 8, 2001.

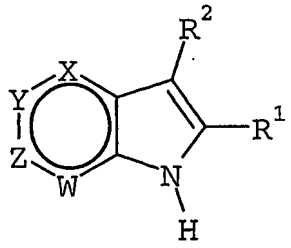
The present invention is directed to the microwave mediated synthesis of heterocyclic compounds, more specifically to the microwave mediated synthesis of substituted bicyclic pyrroles which have utility for the treatment of diseases moderated by the inhibition of protein kinases, particularly FAK, KDR , Syk kinase or Aurora2.

PRIOR ART

Microwave assisted, particularly palladium catalysed, coupling reactions (Hecke, Stille and Suzuki reactions) are disclosed in U. S. Patent No. 6.136,157 to Labwell AB.

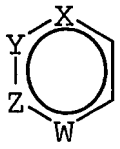
SUMMARY OF THE INVENTION

The present invention provides methods for assisting organic reactions, using microwave energy, to provide good yields of heterocyclic compounds, particularly substituted bicyclic pyrroles of formula (I):



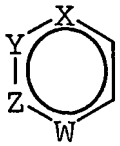
(I)

wherein

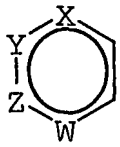


is a six membered aromatic ring in which X represents N or C-R^{10}, Y and Z are each independently selected from CH and CR^3 and W is N; or

is a six membered aromatic ring in which X represents C-R^{10}, Y and W are both N and Z is CR^3; or



is a six membered aromatic ring in which Y represents CR^3, Z and W are both N, and X is N or CR^{10}; or



is a five membered aromatic ring in which (a) Y represents a direct bond, W is N, Z is CR^{12} and X is O, S or NR^{11}, or (b) Y represents a direct bond, W is N, X is CR^{10} and Z is O, S, or NR^{13}, or (c) Y represents a direct bond, W is O, X is CR^{10} and Z is N or CR^{12}, or (d) Y represents a direct bond, W is O, X is N and Z is CR^{12};

R^1 represents aryl or heteroaryl, each optionally substituted by one or more groups selected from alkylenedioxy, alkenyl, alkenyloxy, alkynyl, aryl, cyano, halo, hydroxy, heteroaryl, heterocycloalkyl, nitro, R^4, $-C(=O)-R^9$, $-C(=O)-OR^5$, $-C(=O)-NY^1Y^2$, $-C(=O)-NSO_2-R^7$, $-NY^1Y^2$, $-N(R^6)-C(=O)-R^7$, $-N(R^6)-C(=O)-NY^3Y^4$, $-N(R^6)-C(=O)-OR^7$, $-N(R^6)-SO_2-R^7$, $-N(R^6)-SO_2-NY^3Y^4$, $-SO_2-NY^1Y^2$, $SO_2-NY^1C(=O)-R^7$, and $-Z^1R^9$;

R^2 represents hydrogen, acyl, cyano, halo, lower alkenyl, $-Z^1R^4$, $-SO_2NY^3Y^4$, $-NY^1Y^2$ or lower alkyl optionally substituted by a substituent selected from cyano, heteroaryl, heterocycloalkyl, hydroxy, $-Z^1R^4$, $-C(=O)-NY^1Y^2$, $-CO_2R^8$, $-NY^3Y^4$, $-N(R^6)-C(=O)-R^9$, $-N(R^6)-C(=O)-NY^1Y^2$, $-N(R^6)-C(=O)-OR^7$, $-N(R^6)-SO_2-R^7$, $-N(R^6)-SO_2-NY^3Y^4$, $-SO_2NY^1Y^2$ and one or more halogen atoms;

R^3 represents hydrogen, aryl, cyano, halo, heteroaryl, $-Z^1R^4$, $-C(=O)-OR^5$, $-C(=O)-NY^1Y^2$ or lower alkyl optionally substituted with hydroxy or NY^5Y^6;

R^4 represents alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl or heterocycloalkylalkyl, each optionally substituted by one or more groups selected from aryl, cycloalkyl, cyano, halo, heteroaryl, heterocycloalkyl, hydroxy, -CHO (or a 5-, 6- or 7-membered cyclic acetal derivative thereof), $-C(=O)-NY^1Y^2$, $-C(=O)-OR^5$, $-NY^1Y^2$, $-N(R^6)-C(=O)-R^7$, $-N(R^6)-C(=O)-NY^3Y^4$, $-N(R^6)-SO_2-R^7$, $-N(R^6)-SO_2-NY^3Y^4$, $-Z^1R^7$;

R^5 represents hydrogen, alkyl, alkenyl, aryl, arylalkyl, heteroaryl or heteroarylalkyl;

R^6 represents hydrogen or lower alkyl;

R^7 represents alkyl, aryl, arylalkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl or heterocycloalkylalkyl;

R^8 represents hydrogen or lower alkyl;

R^9 represents aryl or heteroaryl; or alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl or heterocycloalkylalkyl, each optionally substituted by one or more substituents selected from aryl, cycloalkyl, cyano, halo, heteroaryl, heterocycloalkyl, hydroxy -CHO (or a 5-, 6- or 7-membered cyclic acetal derivative thereof), $-C(=O)-NY^1Y^2$, $-C(=O)-OR^5$, $-NY^1Y^2$, $-N(R^6)-C(=O)-R^7$, $-N(R^6)-C(=O)-NY^3Y^4$, $-N(R^6)-SO_2-R^7$, $-N(R^6)-SO_2-NY^3Y^4$ and $-Z^1R^7$;

R^{10} represents H, halo, cyano, hydroxy, nitro, R^4, $-NY^1Y^2$, $-Z^1R^4$, $-C(=O)-OR^5$, $-C(=O)-R^9$, $-C(=O)-NY^1Y^2$, $-N(R^8)-C(=O)-R^4$, $-N(R^8)-C(=O)-NY^1Y^2$, $-N(R^8)-C(=O)-OR^5$, $-SO_2-NY^3Y^4$ or $-N(R^8)-SO_2-R^9$, or R^{10} may be aryl, heteroaryl, alkenyl or alkynyl, each optionally substituted by one or more groups selected from aryl, cyano, halo, hydroxy, heteroaryl, heterocycloalkyl, nitro, $-C(=O)-NY^1Y^2$, $-C(=O)-OR^5$, $-C(=O)NSO_2-R^7$, $-NY^1Y^2$, $-N(R^6)-C(=O)-R^7$, $-N(R^6)-C(=O)-NY^3Y^4$, $-N(R^6)-C(=O)-OR^7$, $-N(R^6)-SO_2-R^7$, $-N(R^6)-SO_2-NY^3Y^4$, $-SO_2-NY^1Y^2$, $-SO_2-NY^1C(=O)-R^7$ and $-Z^1R^9$;

R^{11} represents H, CN, R^4, $-C(=O)-OR^5$, $-C(=O)-NY^1Y^2$, $-C(=O)-R^9$, $-SO_2-NY^3Y^4$, $-SO_2-R^7$, or aryl, heteroaryl, alkenyl or alkynyl, each optionally substituted by one or more groups selected from aryl, cyano, halo, hydroxy, heteroaryl, heterocycloalkyl, nitro,$-C(=O)-NY^1Y^2$, $-C(=O)-OR^5$, $-NY^1Y^2$, $-N(R^6)-C(=O)-R^7$, $-N(R^6)-C(=O)-NY^3Y^4$, $-N(R^6)-C(=O)-OR^7$, $-N(R^6)-SO_2-R^7$, $-N(R^6)-SO_2-NY^3Y^4$, $-SO_2-NY^1Y^2$ and $-Z^1R^4$;

R^{12} represents cyano, H, $-NY^5Y^6$, $-OR^6$, $-SO_2Me$ or lower alkyl optionally substituted with hydroxy or $-NY^5Y^6$;

R^{13} represents H, lower alkyl optionally substituted with hydroxy or NY^5Y^6;

Y^1 and Y^2 are independently hydrogen, alkenyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, or alkyl optionally substituted by one or more groups selected from aryl, halo, heteroaryl, hydroxy, $-C(=O)-NY^3Y^4$, $-C(=O)-OR^5$, $-NY^3Y^4$, $-N(R^6)-C(=O)-R^7$, $-N(R^6)-C(=O)-NY^3Y^4$, $-N(R^6)-SO_2-R^7$, $-N(R^6)-SO_2-NY^3Y^4$ and $-OR^7$; or the group $-NY^1Y^2$ may form a cyclic amine;

Y^3 and Y^4 are independently hydrogen, alkenyl, alkyl, aryl, arylalkyl, cycloalkyl, heteroaryl or heteroarylalkyl; or the group $-NY^3Y^4$ may form a cyclic amine;

Y^5 and Y^6 are independently hydrogen or lower alkyl;

Z^1 represents O or $S(O)_n$; and

n is zero or an integer 1 or 2.

As used above, and throughout the description of the invention, the following terms, unless otherwise indicated, shall be understood to have the following meanings:-

"Acyl" means an H-CO- or alkyl-CO- group in which the alkyl group is as described herein.

"Acylamino" is an acyl-NH- group wherein acyl is as defined herein.

"Alkenyl" means an aliphatic hydrocarbon group containing a carbon-carbon double bond and which may be straight or branched having about 2 to about 15 carbon atoms in the chain. Preferred alkenyl groups have 2 to about 12 carbon atoms in the chain; and more preferably 2 to about 6 carbon atoms (e.g. 2 to 4 carbon atoms) in the chain. "Branched," as used herein and throughout the text, means that one or more lower alkyl groups such as methyl, ethyl or propyl are attached to a linear chain; here a linear alkenyl chain. "Lower alkenyl" means about 2 to about 4 carbon atoms in the chain, which may be straight or branched. Exemplary alkenyl groups include ethenyl, propenyl, n-butenyl, i-butenyl, 3-methylbut-2-enyl, n-pentenyl, heptenyl, octenyl, cyclohexylbutenyl and decenyl.

"Alkenyloxy" is an alkenyl-O- group wherein alkenyl is as defined above. Exemplary alkenyloxy groups include allyloxy.

"Alkoxy" means an alkyl-O- group in which the alkyl group is as described herein. Exemplary alkoxy groups include difluoromethoxy, methoxy, trifluoromethoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy and heptoxy.

"Alkoxycarbonyl" means an alkyl-O-CO- group in which the alkyl group is as described herein. Exemplary alkoxycarbonyl groups include methoxy- and ethoxycarbonyl.

"Alkyl" means, unless otherwise specified, an aliphatic hydrocarbon group which may be straight or branched chain having about 1 to about 15 carbon atoms in the chain, optionally substituted by one or more halogen atoms. Particular alkyl groups have from 1 to about 6 carbon atoms. "Lower alkyl" as a group or part of a lower alkoxy, lower alkylthio, lower alkylsulfinyl or lower alkylsulfonyl group means unless otherwise specified, an aliphatic hydrocarbon group which may be a straight or branched chain having 1 to about 4 carbon atoms in the chain. Exemplary alkyl groups include methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl, t-butyl, n-pentyl, 3-pentyl, heptyl, octyl, nonyl, decyl and dodecyl. Exemplary alkyl groups substituted by one or more halogen atoms include trifluoromethyl.

"Alkylene" means an aliphatic bivalent radical derived from a straight or branched alkyl group, in which the alkyl group is as described herein. Exemplary alkylene radicals include methylene, ethylene and trimethylene.

"Alkylenedioxy" means an -O-alkylene-O- group in which alkylene is as defined above. Exemplary alkylenedioxy groups include methylenedioxy and ethylenedioxy.

"Alkylsulfinyl" means an alkyl-SO- group in which the alkyl group is as previously described. Preferred alkylsulfinyl groups are those in which the alkyl group is C_{1-4}alkyl.

"Alkylsulfonyl" means an alkyl-SO_2- group in which the alkyl group is as previously described. Preferred alkylsulfonyl groups are those in which the alkyl group is C_{1-4}alkyl.

"Alkylsulfonylcarbamoyl" means an alkyl-SO_2-NH-C(=O)- group in which the alkyl group is as previously described. Preferred alkylsulfonylcarbamoyl groups are those in which the alkyl group is C_{1-4}alkyl.

"Alkylthio" means an alkyl-S- group in which the alkyl group is as previously described. Exemplary alkylthio groups include methylthio, ethylthio, isopropylthio and heptylthio.

"Alkynyl" means an aliphatic hydrocarbon group containing a carbon-carbon triple bond and which group may be a straight or branched chain having about 2 to about 15 carbon atoms in the chain. Preferred alkynyl groups have 2 to about 12 carbon atoms in the chain; and more preferably 2 to about 6 carbon atoms (e.g. 2 to 4 carbon atoms) in the chain. Exemplary alkynyl groups include ethynyl, propynyl, n-butynyl, i-butynyl, 3-methylbut-2-ynyl, and n-pentynyl.

"Aroyl" means an aryl-CO- group in which the aryl group is as described herein. Exemplary aroyl groups include benzoyl and 1- and 2-naphthoyl.

"Aroylamino" is an aroyl-NH- group wherein aroyl is as previously defined.

"Aryl" as a group or part of a group denotes: (i) an optionally substituted monocyclic or multicyclic aromatic carbocyclic moiety of about 6 to about 14 carbon atoms, such as phenyl or naphthyl; or (ii) an optionally substituted partially saturated multicyclic aromatic carbocyclic moiety in which an aryl and a cycloalkyl or cycloalkenyl group are fused together to form a cyclic structure, such as a tetrahydronaphthyl, indenyl or indanyl ring. Except where otherwise defined, aryl groups may be

substituted with one or more aryl group substituents, which may be the same or different, where "aryl group substituent" includes, for example, acyl, acylamino, alkoxy, alkoxycarbonyl, alkylenedioxy, alkylsulfinyl, alkylsulfonyl, alkylthio, aroyl, aroylamino, aryl, arylalkyloxy, arylalkyloxycarbonyl, arylalkylthio, aryloxy, aryloxycarbonyl, arylsulfinyl, arylsulfonyl, arylthio, carboxy (or an acid bioisostere), cyano, halo, heteroaroyl, heteroaryl, heteroarylalkyloxy, heteroaroylamino, heteroaryloxy, hydroxy, nitro, trifluoromethyl, $-NY^3Y^4$, $-CONY^3Y^4$, $-SO_2NY^3Y^4$, $-NY^3$-C(=O)alkyl, $-NY^3SO_2$alkyl or alkyl optionally substituted with aryl, heteroaryl, hydroxy, or $-NY^3Y^4$.

"Arylalkyl" means an aryl-alkyl- group in which the aryl and alkyl moieties are as previously described. Preferred arylalkyl groups contain a C_{1-4}alkyl moiety. Exemplary arylalkyl groups include benzyl, 2-phenethyl and naphthlenemethyl.

"Arylalkyloxy" means an arylalkyl-O- group in which the arylalkyl groups is as previously described. Exemplary arylalkyloxy groups include benzyloxy and 1- or 2-naphthalenemethoxy.

"Arylalkyloxycarbonyl" means an arylalkyl-O-CO- group in which the arylalkyl groups is as previously described. An exemplary arylalkyloxycarbonyl group is benzyloxycarbonyl.

"Arylalkylthio" means an arylalkyl-S- group in which the arylalkyl group is as previously described. An exemplary arylalkylthio group is benzylthio.

"Aryloxy" means an aryl-O- group in which the aryl group is as previously described. Exemplary aryloxy groups include phenoxy and naphthoxy, each optionally substituted.

"Aryloxycarbonyl" means an aryl-O-C(=O)- group in which the aryl group is as previously described. Exemplary aryloxycarbonyl groups include phenoxycarbonyl and naphthoxycarbonyl.

"Arylsulfinyl" means an aryl-SO- group in which the aryl group is as previously described.

"Arylsulfonyl" means an aryl-SO_2- group in which the aryl group is as previously described.

"Arylsulfonylcarbamoyl" means an aryl-SO_2-NH-C(=O)- group in which the aryl group is as previously described.

"Arylthio" means an aryl-S- group in which the aryl group is as previously described. Exemplary arylthio groups include phenylthio and naphthylthio.

"Azaheteroaryl" means an aromatic carbocyclic moiety of about 5 to about 10 ring members in which one of the ring members is nitrogen and the other ring members are selected from carbon, oxygen, sulfur, and nitrogen. Examples of azaheteroaryl groups include benzimidazolyl, imidazolyl, indazolinyl, indolyl, isoquinolinyl, pyridyl, pyrimidinyl, pyrrolyl, quinolinyl, quinazolinyl and tetrahydroindolizinyl.

"Cyclic amine" means a 3 to 8 membered monocyclic cycloalkyl ring system wherein one of the ring carbon atoms is replaced by nitrogen and which (i) may also contain a further heteroatom-containing group selected from O, S, SO_2, or NY^7 (where Y^7 is hydrogen, alkyl, aryl, arylalkyl, -C(=O)-R^7, -C(=O)-OR^7 or -SO_2R^7); and (ii) may be fused to additional aryl (e.g. phenyl), heteroaryl (e.g. pyridyl), heterocycloalkyl or cycloalkyl rings to form a bicyclic or tricyclic ring system. Exemplary cyclic amines include pyrrolidine, piperidine, morpholine, piperazine, indoline, pyrindoline, tetrahydroquinoline and the like groups.

"Cycloalkenyl" means a non-aromatic monocyclic or multicyclic ring system containing at least one carbon-carbon double bond and having about 3 to about 10 carbon atoms. Exemplary monocyclic cycloalkenyl rings include cyclopentenyl, cyclohexenyl and cycloheptenyl.

"Cycloalkyl" means a saturated monocyclic or bicyclic ring system of about 3 to about 10 carbon atoms, optionally substituted by oxo. Exemplary monocyclic cycloalkyl rings include C_{3-8}cycloalkyl rings such as cyclopropyl, cyclopentyl, cyclohexyl and cycloheptyl.

"Cycloalkylalkyl" means a cycloalkyl-alkyl- group in which the cycloalkyl and alkyl moieties are as previously described. Exemplary monocyclic cycloalkylalkyl groups include cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl and cycloheptylmethyl.

"Halo" or "halogen" means fluoro, chloro, bromo, or iodo. Preferred are fluoro and chloro.

"Heteroaroyl" means a heteroaryl-C(=O)- group in which the heteroaryl group is as described herein. Exemplary heteroaryl groups include pyridylcarbonyl.

"Heteroaroylamino" means a heteroaroyl-NH- group in which the heteroaryl moiety is as previously described.

"Heteroaryl" as a group or part of a group denotes: (i) an optionally substituted aromatic monocyclic or multicyclic organic moiety of about 5 to about 10 ring members in which one or more of the ring

members is/are element(s) other than carbon, for example nitrogen, oxygen or sulfur (examples of such groups include benzimidazolyl, benzthiazolyl, furyl, imidazolyl, indolyl, indolizinyl, isoxazolyl, isoquinolinyl, isothiazolyl, oxadiazolyl, pyrazinyl, pyridazinyl, pyrazolyl, pyridyl, pyrimidinyl, pyrrolyl, quinazolinyl, quinolinyl, 1,3,4-thiadiazolyl, thiazolyl, thienyl and triazolyl groups, optionally substituted by one or more aryl group substituents as defined above except where otherwise defined); (ii) an optionally substituted partially saturated multicyclic heterocarbocyclic moiety in which a heteroaryl and a cycloalkyl or cycloalkenyl group are fused together to form a cyclic structure (examples of such groups include pyrindanyl groups, optionally substituted by one or more "aryl group substituents" as defined above, except where otherwise defined). Optional substituents include one or more "aryl group substituents" as defined above, except where otherwise defined.

"Heteroarylalkyl" means a heteroaryl-alkyl- group in which the heteroaryl and alkyl moieties are as previously described. Preferred heteroarylalkyl groups contain a C_{1-4}alkyl moiety. Exemplary heteroarylalkyl groups include pyridylmethyl.

Heteroarylalkyloxy" means an heteroarylalkyl-O- group in which the heteroarylalkyl group is as previously described. Exemplary heteroaryloxy groups include optionally substituted pyridylmethoxy.

"Heteroaryloxy" means an heteroaryl-O- group in which the heteroaryl group is as previously described. Exemplary heteroaryloxy groups include optionally substituted pyridyloxy.

"Heteroarylsulfonylcarbamoyl" means a heteroaryl-SO_2-NH-C(=O)- group in which the heteroaryl group is as previously described.

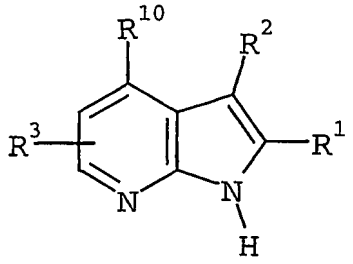
"Heterocycloalkyl" means: (i) a cycloalkyl group of about 3 to 7 ring members which contains one or more heteroatoms or heteroatom-containing groups selected from O, S and NY^7 and mat be optionally substituted by oxo; (ii) a partially saturated multicyclic heterocarbocyclic moiety in which an aryl (or heteroaryl) ring, each optionally substituted by one or more "aryl group substituents," and a heterocycloalkyl group are fused together to form a cyclic structure. (Examples of such groups include chromanyl, dihydrobenzofuranyl, indolinyl and pyrindolinyl groups).

"Heterocycloalkylalkyl" means a heterocycloalkyl-alkyl- group in which the heterocycloalkyl and alkyl moieties are as previously described.

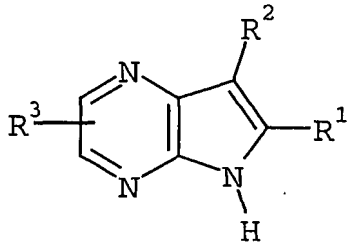
More specifically the present invention is directed to the microwave mediated synthesis of substituted bicyclic pyrroles involving nucleophilic aromatic substitution, biaryl/heterobiaryl coupling and

decarboxylation. These microwave assisted reactions all provide improved rate enhancement and yield over traditional thermal heating methods in the preparation of protein kinase inhibitors or of the intermediates in the preparation thereof.

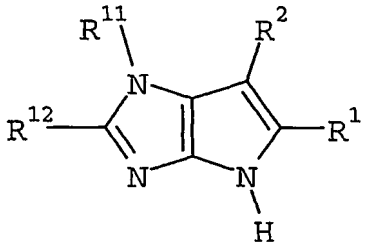
In particular, this invention is directed to processes for the synthesis of 2-aryl and 2-heteroaryl-pyrrolo[2,3-b]-pyridines of formula (Ia), 2-aryl and 2-heteroaryl-pyrrolo[2,3-b]-pyridazines of formula (Ib) and 5-aryl and 5-heteroaryl-pyrrolo[2,3-d]imidazoles of formula (Ic), which processes involve one or more steps that are assisted by the use of microwave energy.



(Ia)



(Ib)

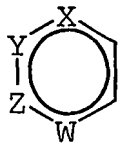


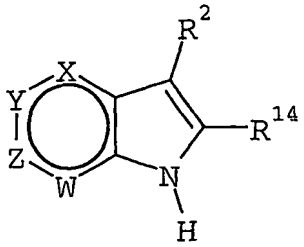
(Ic)

in which R^1, R^2, R^3, R^{10}, R^{11} and R^{12} are as hereinbefore defined.

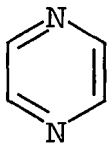
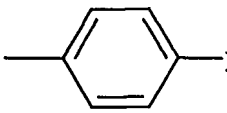
Such compounds have utility for the treatment of diseases moderated by the inhibition of protein kinases, particularly FAK, KDR, Syk kinase or Aurora2.

In the reactions described hereinafter it may be necessary to protect reactive functional groups, for example hydroxy, amino, imino, thio or carboxy groups, where these are desired in the final product, to avoid their unwanted participation in the reactions. Conventional protecting groups may be used in accordance with standard practice, for examples see T.W. Greene and P.G.M.Wuts in "Protective Groups in Organic Chemistry" John Wiley and Sons, 1991.

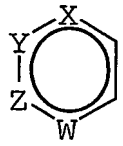
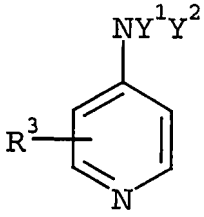
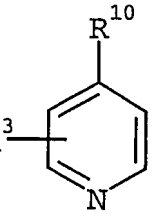
Compounds of formula (1), wherein R^2 and  are as hereinbefore defined, and R^1 is aryl or heteroaryl substituted by $-NY^1Y^2$ (in which Y^1 and Y^2 are as hereinbefore defined), may be prepared by reaction of compounds of formula (II):



(II)

wherein R^{14} is aryl or heteroaryl substituted by $-OSO_2CH_3$ with amines of formula HNY^1Y^2, wherein Y^1 and Y^2 are as hereinbefore defined, in a microwave oven at a temperature at about 200°C. This microwave assisted reaction may conveniently be carried out in a mixture of inert solvents, such as dioxane and dimethylformamide. This reaction is particularly suitable for the preparation of compounds of formula (1), wherein R^2 is as hereinbefore defined,  is  and R^1 is  .

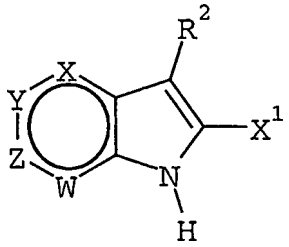
Compounds of formula (1), wherein R^2 and  are as hereinbefore defined, and R^1 is aryl or heteroaryl substituted by $-NY^1Y^2$ (in which Y^1 and Y^2 are as hereinbefore defined), may also be prepared by reaction of compounds of formula (II), wherein R^{14} is aryl or heteroaryl substituted by halo, preferably bromo or iodo, with amines of formula HNY^1Y^2, wherein Y^1 and Y^2 are as hereinbefore defined, in the presence ofcopper (I) iodide and sodium carbonate, in a microwave oven at a temperature at about 200°C. This microwave assisted reaction may conveniently be carried out in an inert solvent, such as dimethylformamide.

Compounds of formula (1), wherein R^1 and R^2 are as hereinbefore defined, and  is  (in which R^3, Y^1 and Y^2 are as hereinbefore defined), may be prepared by reaction of the corresponding compounds of formula (1), wherein  is  in which R^{10} is halo, preferably bromo or iodo, with amines of formula HNY^1Y^2, wherein Y^1 and Y^2 are as hereinbefore defined, in a microwave oven at a temperature at about 210°C. This microwave assisted reaction may conveniently be carried out in an inert solvent, such as α,α,α-trifluorotoluene.

Compounds of formula (1), wherein R^2 and  are as hereinbefore defined, and R^1 is aryl or heteroaryl substituted by aryl or heteroaryl, may be prepared by reaction of the corresponding compounds of formula (1), wherein R^1 is aryl or heteroaryl substituted by halo, preferably bromo or

iodo, with the appropriate aryl- or heteroaryl-boronic acid, in the presence of tetrakis(triphenylphosphine)palladium(0) and aqueous sodium carbonate, in a microwave oven at a temperature at about 180°C. This microwave assisted reaction may conveniently be carried out in an inert solvent, such as dioxane.

Compounds of formula (1), wherein R^2 and  are as hereinbefore defined, and R^1 is aryl or heteroaryl substituted by aryl or heteroaryl, may be prepared by reaction of compounds of formula (III):-



(III)

wherein R^2 and  are as hereinbefore defined, and X^1 is iodo, with the appropriate aryl- or heteroaryl-boronic acid, in the presence of tetrakis(triphenylphosphine)palladium(0) and aqueous sodium hydrogen carbonate, in a microwave oven at a temperature at about 60°C. This microwave assisted reaction may conveniently be carried out in an inert solvent, such as dimethylformamide.

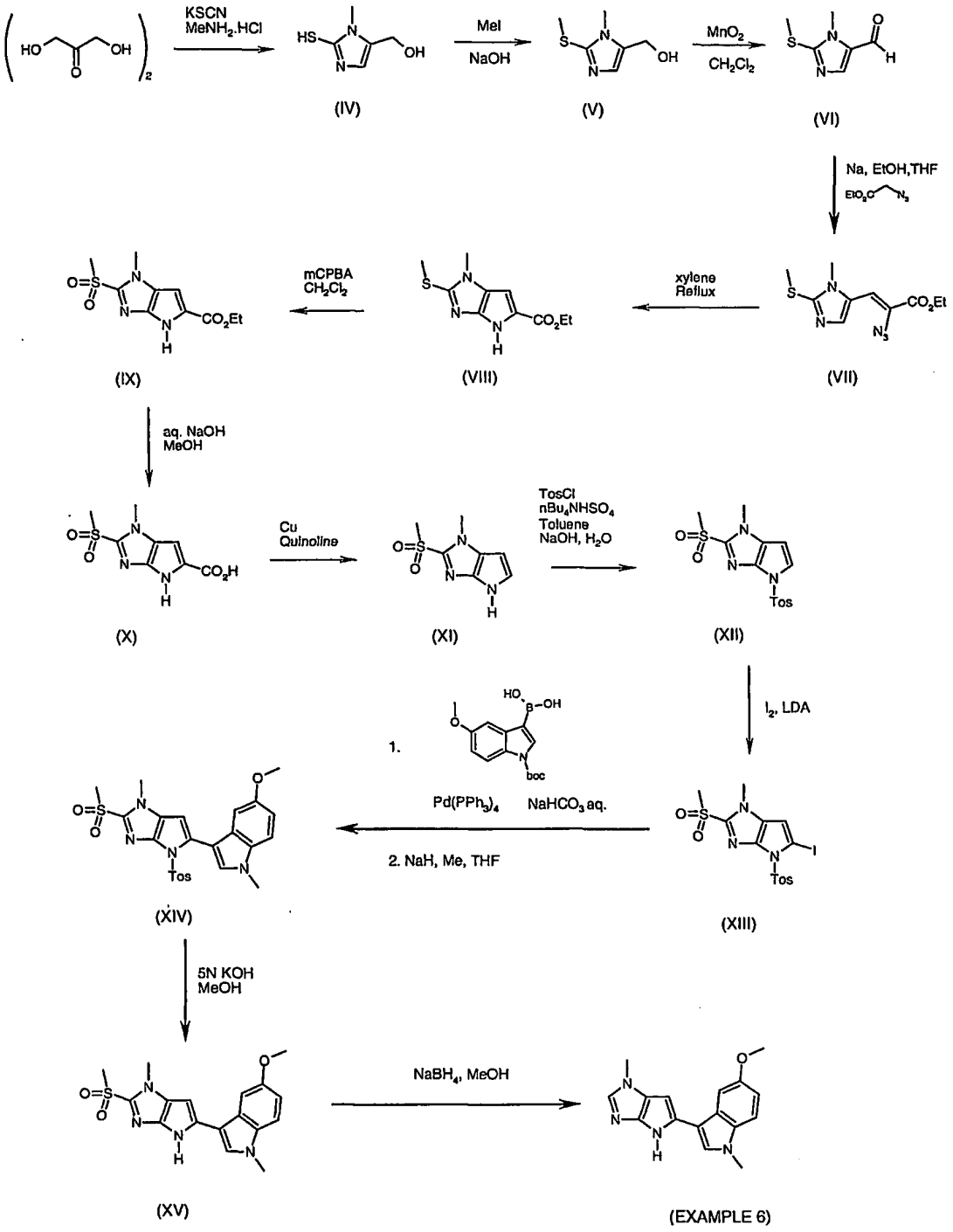
Intermedaites of formula (III) wherein R^2 and  are as hereinbefore defined, and X^1 is iodo

may be prepared by treatment of compounds of formula (III), wherein R^2 and  are as

hereinbefore defined, and X^1 is hydrogen, with lithium diisopropylamide in tetrahydrofuran, at about -78°C, followed by reaction of the resulting anion with iodine.

Intermediates in the synthesis of compounds of formula (I) may also be prepared using microwave mediated reactions. For example the intermediate (XI) in the preparation of Example 6 in scheme (1) may be prepared by decarboxylation of 2-methylsulfonyl-1-methylpyrrolo[2,3-d]imidazole-5-carboxylic acid (V) in the presence of copper in quinoline in a microwave oven. This microwave assisted reaction may conveniently be carried out at about 250°C.

SCHEME 1



The present invention is further exemplified but not limited by the following Illustrative Examples and Reference Examples. In these examples:

400M Hz ^1H nuclear magnetic resonance spectra (NMR) were recorded on a Varian Unity INOVA machine. In the nuclear magnetic resonance spectra (NMR) the chemical shifts (δ) are expressed in ppm relative to tetramethylsilane. Abbreviations have the following significances: s = singlet; d = doublet; t = triplet; m = multiplet; q = quartet; dd = doublet of doublets; ddd = doublet of double doublets.

High Pressure Liquid Chromatography - Mass Spectrometry (LC-MS) conditions for determination of retention times (R_T) were as follows:-

METHOD A: YMC ODS-A HPLC column (50mm x 4mm) operated under gradient elution conditions with mixtures of water and acetonitrile, (A) 95:5 and (B) 5:95, containing 0.1% formic acid as the mobile phase gradient (0.00 minutes, 95%A:5%B; linear gradient to 100% B at 2 minutes; then hold until 3.4 minutes); flow rate 2ml/minute with approximately 200µl/minute split to the Mass Spectrometer; injection volume 10-40µl; in line Diode Array (220-450nm), in line Evaporative light scattering (ELS) detection ELS - temperature 50°C, Gain 8 - 1.8ml/minute; Source temperature 150°C;

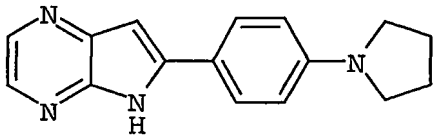
METHOD B: 3 micron Luna C18 (2) HPLC column (30mm x 4.6mm) operated under gradient elution conditions with mixtures of (A) water containing 0.1% trifluoroactic acid and (B) acetonitrile containing 0.1% trifluoroacetic acid as the mobile phase gradient : 0.00 minutes, 95%A:5%B; 0.50 minutes, 95%A:5%B; 4.50 minutes, 5%A:95%B; 5.00 minutes, 5%A:95%B; 5.50 minutes, 95%A:5%B; flow rate 2ml/minute with approximately 200µl/minute split to the Mass Spectrometer; injection volume 10-40µl; in line Diode Array (220-450nm), in line Evaporative light scattering (ELS) detection ELS - temperature 50°C, Gain 8 - 1.8ml/minute; Source temperature 150°C.

The high pressure liquid chromatography retention times (HPLC: R_T values) were determined by:- (i) Method A, C18 Phenomenex (150 x 4.6mm) column using gradient elution with a mixture of acetonitrile and water with 0.1% trifluoroacetic acid as the mobile phase (0-1 minute 5% acetonitrile; 1-12 minutes ramp up to 95% acetonitrile; 12-14.95 minutes 95% acetonitrile; 14.95-15 minutes 0% acetonitrile); or Method B, YMC ODS-AQ (2 X 50mm) column using gradient elution with a mixtures of acetonitrile and water with 0.1% formic acid as the mobile phase [95/5/0.1% (A) to 5/95/0.1% (B)] and a flow rate of 0.4 mL/minute); or Method C, 3 micron BDS C18 Hypersil (50 x 4.6 mm) using gradient elution with a mixture of acetonitrile and water with 0.1% formic acid as the mobile phase (95 / 5 / 0.1%, water / acetonitrile / formic acid for 0.1 minute linear gradient to 5 / 95 / 0.1%, water / acetonitrile / formic acid at 2 minutes and hold until 3.5 minutes).

The thin layer chromatography (TLC) R_F values were determined using Merck silica plates.

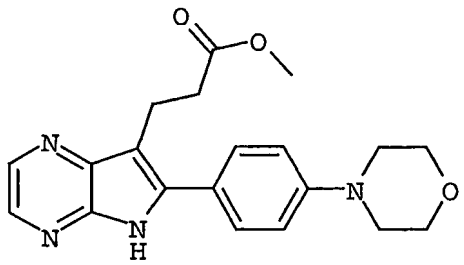
EXAMPLE 1

(a) 6-(4-pyrrolidinophenyl)-5H-pyrrolo[2,3-b]pyrazine



A microwave tube (Smith process vial, 2-5ml) was charged with 6-(4-trifluorosulfonyloxyphenyl)-5H-pyrrolo[2,3-b]pyrazine [20mg, Reference Example 1(a)], pyrrolidine (2.39mM), dioxane (3ml) and dimethylformamide (0.5ml). The tube was capped and the resulting mixture was heated at 200°C in a microwave oven for 1 hour after which the 6-(4-trifluorosulfonyloxyphenyl)-5H-pyrrolo[2,3-b]pyrazine had been consumed. The reaction mixture was evaporated and the residue was triturated with a mixture of ethyl acetate and methanol (9:1, v/v). The solid was filtered and then dried under vacuum to give the 6-(4-pyrrolidinophenyl)-5H-pyrrolo[2,3-b]pyrazine (11mg) as a yellow solid. MS: 265.1(MH^+). HPLC: R_T = 2.92 minutes.

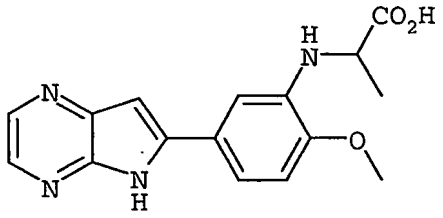
(b) Methyl 3-[6-(4-morpholinophenyl)-5H-pyrrolo[2,3-b]pyrazin-7-yl]- propionate



By proceeding in a similar manner to Example 1 but using methyl 3-[6-(4-trifluoromethylsulfonyloxy-phenyl)-5H-pyrrolo[2,3-b]pyrazin-7-yl]-propionate [Reference Example 1(b)] and morpholine heated at 200°C for 3 hours and subjecting the residue to chromatography on silica eluting with ethyl acetate there was prepared methyl 3-[6-(4-morpholinophenyl)-5H-pyrrolo[2,3-b]pyrazin-7-yl]- propionate as a yellow solid. MS: 367.2(MH^+). HPLC: R_T = 0.75 minutes.

EXAMPLE 2

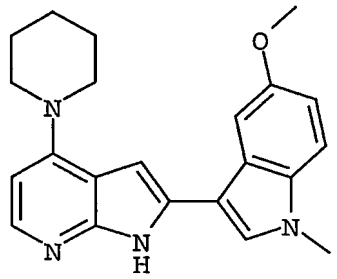
2-[5-(5H-Pyrrolo[2,3-b]pyrazin-6-yl)-2-methoxyphenyl)-]aminopropionic acid



A microwave tube (Smith process vial, 2-5ml) was charged with 6-(3-bromo-4-methoxyphenyl)-5H-pyrrolo[2,3-b]pyrazine [50mg, Reference Example 2(b)], alanine (148mg), dimethylformamide (3ml), copper(I) iodide (3.2mg) and sodium carbonate (27mg). The tube was capped and the resulting mixture was heated at 200°C in a microwave oven for 2 hours. Water was added and the reaction mixture was extracted with ethyl acetate. The organic layer was washed with water, then with brine, then dried over magnesium sulfate and then concentrated under vacuum. The residue was subjected to column chromatography on silica eluting with a mixture of ethyl acetate and heptane (1/1, v/v) to give 2-[5-(5H-pyrrolo[2,3-b]pyrazin-6-yl)-2-methoxyphenyl)-]aminopropionic acid (11mg) as a yellow solid. MS: 313.1(MH^+). HPLC R_T = 3.04 minutes.

EXAMPLE 3

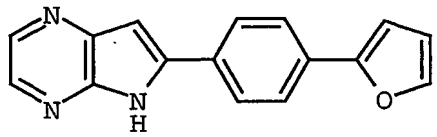
4-Piperidino-2-(5-methoxy-1-methyl-1H-indol-3-yl)-1H-pyrrolo[2,3-b]pyridine



A microwave tube (Smith process vial, 2-5ml) was charged with 4-chloro-2-(5-methoxy-1-methyl-1H-indol-3-yl)-1H-pyrrolo[2,3-b]pyridine (4mg, Reference Example 9), piperidine (220µl) and α, α, α-trifluorotoluene (3.5ml) . The tube was-capped and the resulting mixture was heated at 210°C in a microwave oven for 280 minutes. The reaction mixture was evaporated to give 4-piperidino-2-(5-methoxy-1-methyl-1H-indol-3-yl)-1H-pyrrolo[2,3-b]pyridine. MS: 361.1 (MH^+). HPLC R_T =4.74 minutes .

EXAMPLE 4

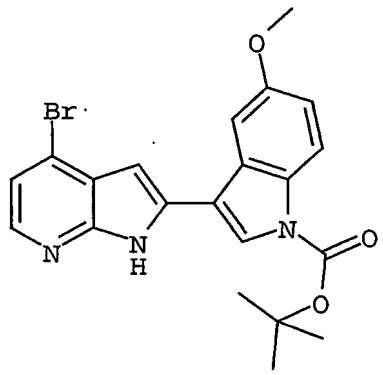
6-(4-(Furan-2-yl)phenyl)-5H-pyrrolo[2,3-b]pyrazine



A mixture of 6-(4-trifluoromethylsulfonyloxyphenyl)-5H-pyrrolo[2,3-b]pyrazine [20mg, Reference Example 1(a)], dioxane (2.5mL), furan-2-boronic acid (9.8mg), sodium carbonate solution (0.06mL, 2N), and tetrakis(triphenylphosphine)palladium[0] (4mg) was heated at 180°C in a microwave oven for 40 minutes. The reaction mixture was then evaporated and the residue was subjected to chromatography on silica eluting with a mixture of ethyl acetate and pentane (1:1, v/v) to give, after trituration with a mixture of ethyl acetate and methanol, 6-(4-(furan-2-yl)phenyl)-5H-pyrrolo[2,3-b]pyrazine (7mg) as a yellow solid. MS: 262.1(MH^+). R_T = 3.05 minutes.

EXAMPLE 5

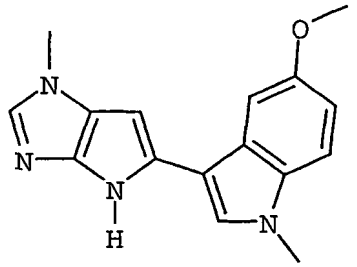
4-Bromo-2-(5-methoxy-1-carboxylic acid tert-butyl ester-1H-indol-3-yl)-1H-pyrrolo[2,3-b]pyridine



is prepared by treating 4-bromo-2-(5-methoxy-1-carboxylic acid tert-butyl ester-1H-indol-3-yl)-1-(toluene-4-sulfonyl)-1H-pyrrolo[2,3-b]pyridine (Reference Example 16) with 5N potassium hydroxide in methanol.

EXAMPLE 6

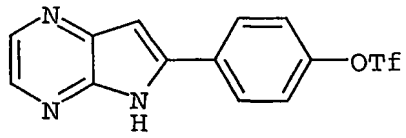
5-(5-methoxy-1-methyl-1H-indol-3-yl)-1methyl-1H-pyrrolo[2,3-d]imidazole



is prepared by treating 5-(5-methoxy-1-methyl-1H-indol-3-yl)-1methyl-2-methylsulfonyl-1H-pyrrolo[2,3-d]imidazole (Reference Example 19) with sodium borohydride in methanol.

REFERENCE EXAMPLE 1

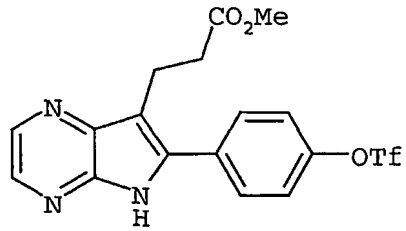
(a) 6-(4-trifluoromethylsulfonyloxyphenyl)-5H-pyrrolo[2,3-b]pyrazine



A suspension of using 6-(4-hydroxyphenyl)-5H-pyrrolo[2,3-b]pyrazine [150mg, Reference Example 2(a)] in dichloromethane (40mL) and dimethylformamide (20ml), cooled to -78°C under a nitrogen atmosphere, was treated with triethylamine (0.2ml) followed by N-phenylyltrifluormethanesulfonimide (510mg). The resultant mixture was allowed to warm slowly to ambient temperature, stirring was continued for a further 12 hours then saturated sodium bicarbonate (20mL) was added. The organic phase was separated and the aqueous phase was extracted twice with dichloromethane (20mL). The combined organics were dried over sodium sulfate then evaporated. The residue was subjected to flash column chromatography on silica eluting with a mixture of ethyl acetate and pentane (2:3, v/v) to give the 6-(4-trifluoromethylsulfonyloxyphenyl)-5H-pyrrolo[2,3-b]pyrazine (44mg) as a cream solid.

MS: 344(MH^+).

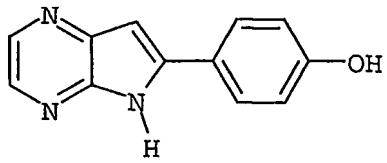
(b) methyl 3-{6-(4-trifluoromethylsulfonyloxyphenyl)-5H-pyrrolo[2,3-b]pyrazin-7-yl}propionate



By proceeding in a similar manner to Reference Example 1 above but using methyl 3-[6-(4-hydroxy-phenyl)-5H-pyrrolo[2,3-b]pyrazin-7-yl]-propionate [Reference Example 3] there was prepared methyl 3-[6-(4-trifluoromethylsulfonyloxyphenyl)-5H-pyrrolo[2,3-b]pyrazin-7-yl]-propionate as a white solid. MS: 430(MH^+). HPLC: (MethodC): R_T = 5.39 minutes.

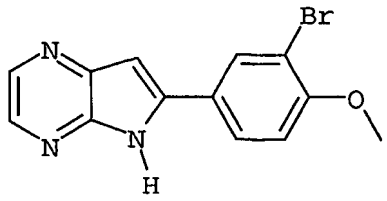
REFERENCE EXAMPLE 2

(a) 6-(4-Hydroxyphenyl)-5H-pyrrolo[2,3-b]pyrazine



A stirred solution of diisopropylamine (13.8ml) in tetrahydrofuran (140mL), at -15°C and under nitrogen, was treated with a solution of n-butyllithium in hexanes (39.2mL, 1.6M) over 25 minutes, whilst maintaining the temperature below -10°C. After stirring for 30 minutes the mixture was treated with methylpyrazine (4ml) over 15 minutes, then stirred for 1 hour and then treated with a solution of 4-cyanophenol (5.2g) in tetrahydrofuran (60mL) over 1 hour, keeping the temperature below -10°C. The reaction mixture was allowed to warm to room temperature over 2 hours, then stood overnight and then treated with water (60 mL). The tetrahydrofuran was removed in vacuo and the resultant mixture was partitioned between ethyl acetate (50mL) and water (50mL). The two layers were separated, and the aqueous layer was extracted with ethyl acetate (50mL). The combined organics were washed with water (50mL) and then evaporated. The residue was triturated with ethyl acetate. The resulting solid was filtered and then dried under vacuum to give 6-(4-hydroxyphenyl)-5H-pyrrolo[2,3-b]pyrazine (376 mg) as a pale yellow solid. MS: 212(MH^+).

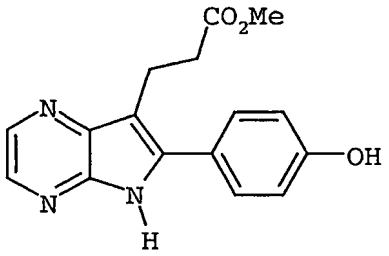
(b) 6-(3-bromo-4-methoxyphenyl)-5H-pyrrolo[2,3-b]pyrazine,



By proceeding in a manner similar to Reference Example 2(a) above but using 3-bromo-4-methoxybenzonitrile, there was prepared 6-(3-bromo-4-methoxyphenyl)-5H-pyrrolo[2,3-b]pyrazine as a yellow solid. MS: 304(MH^+). HPLC: R_T =2.37 minutes.

REFERENCE EXAMPLE 3

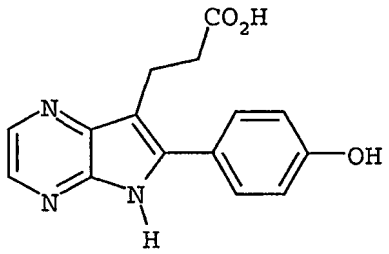
Methyl 3-{6-(4-hydroxyphenyl)-5H-pyrrolo[2,3-b]pyrazin-7-yl}propionate



A solution of 3-{6-(4-hydroxyphenyl)-5H-pyrrolo[2,3-b]pyrazin-7-yl}propionic acid (0.02g, Reference Example 4) in methanol (2mL) was treated with a catalytic amount of paratoluenesulfonic acid. The mixture was refluxed for 4 hours, the solvent removed by evaporation and the precipitate filtered. The solid was then taken in ethyl acetate, the organic layer washed with water, brine, dried over magnesium sulfate and evaporated to give a yellow solid which was subjected to flash chromatography on silica, eluting with ethyl acetate) to give methyl 3-{6-(4-hydroxyphenyl)-5H-pyrrolo[2,3-b]pyrazin-7-yl}propionate. MS: 298(MH^+). HPLC (MethodC): R_T = 2.58 minutes.

REFERENCE EXAMPLE 4

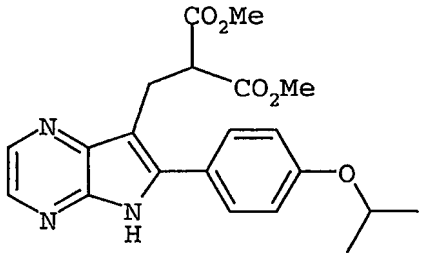
3-{6-(4-Hydroxyphenyl)-5H-pyrrolo[2,3-b]pyrazin-7-yl}propionic acid



To a solution of dimethyl 3-[6-(4-(1-methyl)ethoxyphenyl)-5H-pyrrolo[2,3-b]pyrazin-7-yl]-propionic 1,1-diacid 1,1-dicarboxylate [0.77g, Reference Example 5] in methanol (45mL) was added 1N sodium hydroxide solution (7.7mL). The reaction mixture was heated at 50°C for 6 hours then allowed to stand at room temperature overnight. The solvent was removed by evaporation, 6N sulfuric acid solution (20mL) was added and the reaction mixture refluxed for 12 hours. After cooling, the solution was basified to pH 4 with 4N sodium hydroxide solution and the resultant precipitate filtered and dried under vacuum to afford 3-{6-(4-hydroxyphenyl)-5H-pyrrolo[2,3-b]pyrazin-7-yl}propionic acid (0.42g) as a yellow solid which was used without further purification. MS: 284(MH^+). HPLC (Method C): R_T = 2.3 minutes.

REFERENCE EXAMPLE 5

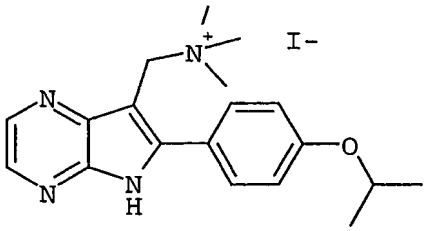
Dimethyl 3-[6-(4-(1-methyl)ethoxyphenyl)-5H-pyrrolo[2,3-b]pyrazin-7-yl]-propionic 1,1-diacid 1,1-dicarboxylate



To a solution of dimethyl malonate (0.46g) dissolved in N-methylpyrrolidinone (10mL) at 0°C under nitrogen was added sodium hydride (0.14g). After 10 minutes, a solution of [6-(4-(1-methyl)ethoxy)-phenyl-5H-pyrrolo[2,3-b]pyrazin-7-yl]methyltrimethyl ammonium iodide (0.39g, Reference Example 6) was added and the reaction mixture was warmed to room temperature and allowed to stir for 3 hours. The reaction mixture was poured into water (50mL) and extracted three times with ethyl acetate (50mL). The combined organic fractions were dried over magnesium sulfate and then evaporated. The residue was subjected to flash column chromatography on silica eluting with a mixture of ethyl acetate and heptane (1:1, v/v) to give dimethyl 3-[6-(4-(1-methyl)ethoxyphenyl)-5H-pyrrolo[2,3-b]pyrazin-7-yl]-propionic 1,1-diacid 1,1-dicarboxylate (0.25g) as a beige solid. MS: 398(MH^+). ^1H NMR[$CDCl_3$]: δ 10.1(broad s, 1H); 8.41(d, 1H, J=2.3 Hz); 8.16(d, 1H, J=2.3 Hz); 7.62(d, 2H, J=8.21 Hz); 7.03(d, 2H, J=8.20 Hz); 4.64(m, 1H); 4.45(t, 1H); 3.78(d, 1H); 3.60(s, 6H); 1.41(d, 6H, J=4.41 Hz).

REFERENCE EXAMPLE 6

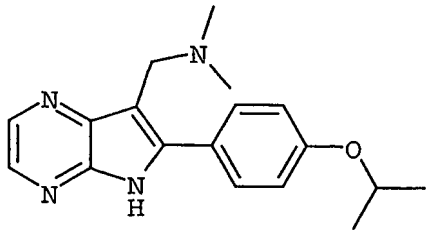
[6-(4-(1-Methyl)ethoxy)phenyl-5H-pyrrolo[2,3-b]pyrazin-7-yl]methyltrimethyl ammonium iodide



To a solution of 6-(4-(1-methyl)ethoxy)phenyl-5H-pyrrolo[2,3-b]pyrazin-7-yl]methyldimethylamine [1g, Reference Example 7] in tetrahydrofuran (50mL) under nitrogen at 40°C was added methyl iodide (5.6mL). The reaction mixture was stirred for 4 hours and the solvent was evaporated. The residue was chased with toluene (30mL) and dried under vacuum to afford [6-(4-(1-methyl)ethoxy)phenyl-5H-pyrrolo[2,3-b]pyrazin-7-yl]methyltrimethyl ammonium iodide as a beige solid which was used immediately without further purification.

REFERENCE EXAMPLE 7

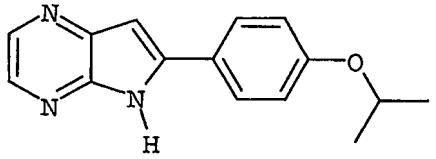
6-(4-(1-Methyl)ethoxy)phenyl-5H-pyrrolo[2,3-b]pyrazin-7-yl]methyl-dimethylamine



To a solution of dimethylamine (4.93 mL of a 2M solution in tetrahydrofuran) and acetic acid (0.65mL) at 0°C was added formaldehyde (0.77mL of a 40% aqueous solution). The reaction mixture was stirred for 10 minutes. A solution of 6-[4-(1-methyl)ethoxyphenyl]-5H-pyrrolo[2,3-b]pyrazine [1g, Reference Example 8] in tetrahydrofuran (75mL) was added and the reaction mixture allowed to stir at room temperature overnight. The reaction mixture was washed with 1N sodium hydroxide solution, brine, dried over magnesium sulfate and evaporated in vacuo. The residue was subjected to flash column chromatography on silica eluting with a mixture of tetrahydrofuran and methanol (1:1, v/v) to give 6-(4-(1-methyl)ethoxy)phenyl-5H-pyrrolo[2,3-b]pyrazin-7-yl]methyl-dimethylamine (1.1g) as a beige solid.

REFERENCE EXAMPLE 8

6-[4-(1-methyl)ethoxyphenyl]-5H-pyrrolo[2,3-b]pyrazine

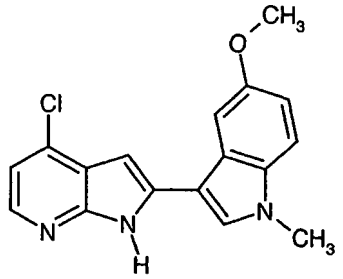


By proceeding in a manner similar to Reference Example 1 but using 4-(1-methyl)-ethoxybenzonitrile, there was prepared 6-[4-(1-methyl)ethoxyphenyl]-5H-pyrrolo[2,3-b]pyrazine as a yellow solid.

MS: 254(MH^+). HPLC (METHOD B): R_T = 1.64 minutes.

REFERENCE EXAMPLE 9

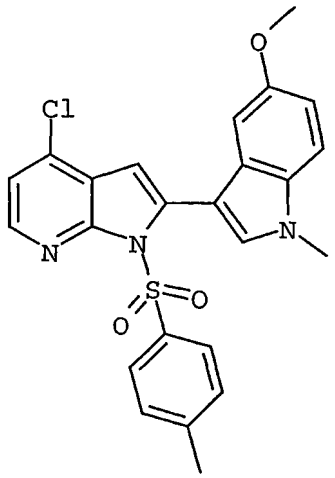
4-Chloro-2-(5-methoxy-1-methyl-1H-indol-3-yl)-1H-pyrrolo[2,3-b]pyridine



A solution of 4-chloro-2-(5-methoxy-1-methyl-1H-indol-3-yl)-1-(toluene-4-sulfonyl)-1H-pyrrolo[2,3-b]pyridine (1g, Reference Example 10) in 50ml of methanol was treated with 5N potassium hydroxide (5ml). The reaction mixture was refluxed for 4 hours then concentrated under vacuum. The residue was dissolved in the minimum amount of water (25ml) and the pH was adjusted to 4 with concentrated hydrochloric acid. The precipitate was filtered, washed with water and dried under vacuum to give 4-chloro-2-(5-methoxy-1-methyl-1H-indol-3-yl)-1H-pyrrolo[2,3-b]pyridine (440mg) as a yellow solid, m.p. 262-263°C. MS: 312(MH^+).

REFERENCE EXAMPLE 10

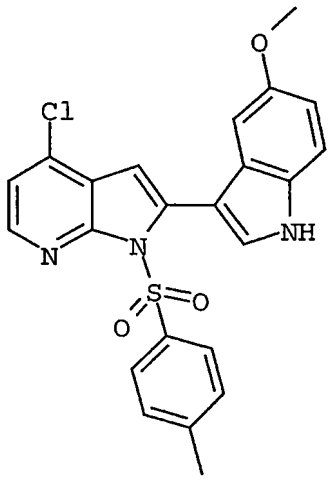
4-Chloro-2-(5-methoxy-1-methyl-1H-indol-3-yl)-1-(toluene-4-sulfonyl)-1H-pyrrolo[2,3-b]pyridine



A solution of 4-chloro-2-(5-methoxy-1H-indol-3-yl)-1-(toluene-4-sulfonyl)-1H-pyrrolo[2,3-b] pyridine [6.6g, Reference Example 11] in dimethylformamide (100mL), under a nitrogen atmosphere, was treated with sodium hydride (700mg, 60% dispersion in oil). After stirring at ambient temperature for 30 minutes the mixture was treated dropwise with ethyl chloroacetate (2.0mL) and stirring was continued for an additional 4 hours. The reaction mixture was evaporated and the residue was partitioned between ethyl acetate and water. The organic phase was washed with brine, then dried over sodium sulfate and then evaporated to give 4-chloro-2-(5-methoxy-1-methyl-1H-indol-3-yl)-1-(toluene-4-sulfonyl)-1H-pyrrolo[2,3-b]pyridine (5.77g) as an off white solid, MS: 466(MH^+). ^1H NMR ($CDCl_3$): δ 8.35 (d,1H); 7.56 (d, 2H), 7.39 (s, 1H); 7.16-7.3 (m, 2H), 7.05 (d, 2H), 6.95-7.0 (m, 2H) 6.6 (s, 1H) 3.9 (s,3H) 3.8 (s, 3H) 2.3 (s, 3H).

REFERENCE EXAMPLE 11

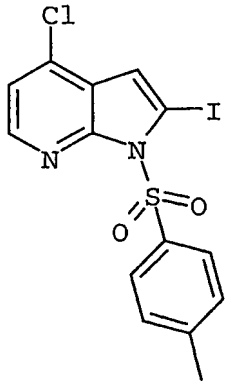
4-Chloro-2-(5-methoxy-1H-indol-3-yl)-1-(toluene-4-sulfonyl)-1H-pyrrolo[2,3-b] pyridine



A solution of 5-methoxy-indole-2-boronic acid (1.18g) in dimethylformamide (50mL) was treated with 4-chloro-2-iodo-1-(toluene-4-sulfonyl)-1H-pyrrolo[2,3-b]pyridine [1.75g, Reference Example 12), then with saturated aqueous sodium bicarbonate (20mL) and then with tetrakis(triphenylphosphine)palladium[0] (0.25g). The mixture was heated at reflux for 1 hour then 15ml of dimethylformamide were added to dissolve the precipitated solid. The reaction mixture was stirred at 125°C for futher 6 hours then allowed to cool to ambient temperature then concentrated to remove the dimethylformamide. The residue was partitioned between water (60 mL) and ethyl acetate (120mL) and the aqueous was extracted twice with ethyl acetate (50mL). The combined organics were dried over sodium sulfate then evaporated. The residual dark oil was subjected to column chromatography on silica eluting with a mixture of ethyl acetate and heptane (1/4, v/v) to give 4-chloro-2-(5-methoxy-1H-indol-3-yl)-1-(toluene-4-sulfonyl)-1H-pyrrolo[2,3-b] pyridine (970mg) as a white solid. MS: 452 (MH^+). ^1H NMR ($CDCl_3$): δ 8.4 (d, 1H), 7.6 (d, 2H), 7.5 (s, 1H), 7.35 (d, 1H), 7.2 (d, 2H), 6.9 (m, 2H), 6.7 (s, 1H), 3.8 (s, 3H), 2.3 (s, 3H).

REFERENCE EXAMPLE 12

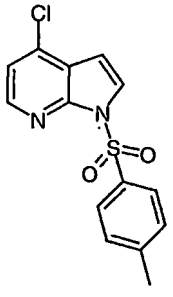
4-chloro-2-iodo-1-(toluene-4-sulfonyl)-1H-pyrrolo[2,3-b]pyridine



A stirred solution of diisopropylamine (1.54mL) in tetrahydrofuran (20mL), at –70°C and under nitrogen, was treated with a solution of n-butyllithium in hexanes (7mL, 1.6M) over 5 minutes, whilst maintaining the temperature below –65°C. After stirring for 20 minutes the mixture was added, at -70°C, to a solution 4-chloro-1-(toluene-4-sulfonyl)-1H-pyrrolo[2,3-b]pyridine [3.06g, ReferenceExample 13(a)] in tetrahydrofuran (70mL) and stirred at –70°C for 45 minutes. A solution of iodine (2.66g) in tetrahydrofuran (10 mL) was then added at –70°C. The reaction mixture was allowed to warm up to room temperature over 1 hour, and stirred for 1 hour and then treated with water (10mL). The reaction mixture was evaporated in vacuo and the residue partitioned between ethyl acetate (150mL) and sodium thiosulphate (2x15mL). The oganic layer was dried over sodium sulfate and then evaporated to dryness. The compound was subjected to column chromatography on silica eluting with a mixture of ethyl acetate and heptane (3/2, v/v) to give 4-chloro-2-iodo-1-(toluene-4-sulfonyl)-1H-pyrrolo[2,3-b]pyridine (1.75g) as a yellow solid. MS: 432(MH^+). ^1H NMR ($CDCl_3$): δ 8.25 (d, 1H), 8.05 (d, 2H), 7.3 (d, 2H), 7.15 (d, 1H), 7.1 (s, 1H), 2.4 (s,3H).

REFERENCE EXAMPLE 13

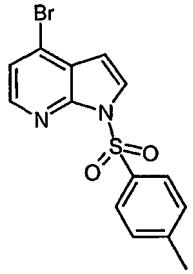
(a) 4-Chloro-1-(toluene-4-sulfonyl)-1H-pyrrolo[2,3-b]pyridine



To a solution of 4-chloro-1H-pyrrolo[2,3-b]pyridine (10.5g, Reference Example 14), *para*-toluenesulfonyl chloride (14.43g) and a catalytic amount of tetrabutylammoniun sulfate (100mg) in dry toluene (200 mL) was added sodium hydroxide (45g in 180mL of water). The biphasic solution was stirred at ambient temperature for 3 hours then extracted twice with ethyl acetate (150mL). The

combined extracts were dried over magnesium sulfate then concentrated under vacuo. Residue was subjected to column chromatography on silica euting with a mixture of ethyl acetate and heptane (3/7, v/v) to give 4-chloro-1-(toluene-4-sulfonyl)-1H-pyrrolo[2,3-b]pyridine (13.8g) as a white solid, MS: 307(MH^+). ^1H NMR ($CDCl_3$): δ 8.3 (d, 1H), 8.05 (d, 2H), 7.8 (d,1H), 7.3 (d, 2H), 7.2 (d, 1H), 6.7 (d, 1H), 2.4 (s, 3H).

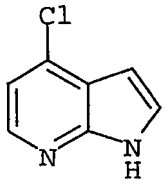
(b) 4-bromo-1-(toluene-4-sulfonyl)-1H-pyrrolo[2,3-b]pyridine



By proceeding in a manner similar to Reference Example 13(a) above but using 4-bromo-1H-pyrrolo[2,3-b]pyridine (Reference Example 18) there was prepared 4-bromo-1-(toluene-4-sulfonyl)-1H-pyrrolo[2,3-b]pyridine as a white solid. MS: 353(MH^+). HPLC: R_T = 5.97 minutes.

REFERENCE EXAMPLE 14

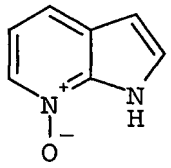
4-Chloro-1H-pyrrolo[2,3-b]pyridine



1H-Pyrrolo[2,3-b]pyridine-N-oxide (10.0g, Reference Example 15) in phosphorous oxychloride (75mL) was heated at reflux for 8 hours. The excess phosphorous oxychloride was evaporated and the residue was taken up in water and the solution was brought to a pH=8-9, the resultant precipitate was filtered and air-dried to give 4-chloro-1H-pyrrolo[2,3-b]pyridine as an off –white solid (10.2g). MS: 152(MH^+). ^1H NMR ($CDCl_3$): δ 8.2 (d, 1H), 7.5 (d,,1H), 7.2 (d, 2H), 6.6 (d, 2H).

REFERENCE EXAMPLE 15

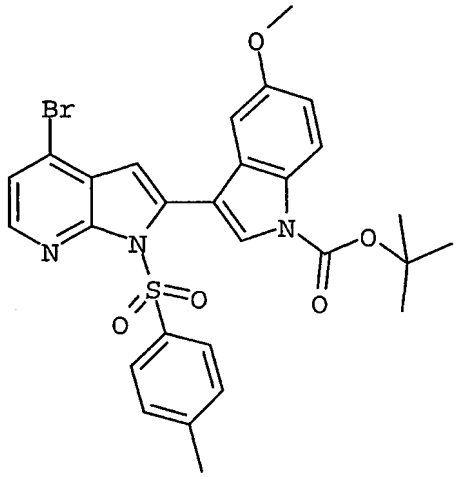
1H-Pyrrolo[2,3-b]pyridine-7-oxide



A solution of 3-chloroperbenzoic acid (224.3g) in dichloromethane (1500mL) was cooled to 0°C. To this a solution of 1H-pyrrolo[2,3-b]pyridine (59.1g) in dichloromethane (500mL) was added dropwise over 30 minutes. The reaction mixture was stirred at room temperature for 1 hour. The solution was concentrated, diluted with methanol (1500mL) and treated with 10% potassium carbonate in water (300mL). The slurry was filtered and the filtrate was evaporated to dryness. The residue was chromatographed on neutral alumina eluting with 20 % methanol in dichloromethane to give 1H-pyrrolo[2,3-b]pyridine-7-oxide as a tan solid (47.0g). MS: 135(MH^+). ^{1}HNMR ($CDCl_3$): δ 13.1 (s, 1H), 8.2 (d,1H), 7.65 (d, 1H), 7.4 (d, 1H), 7.0 (m, 1H), 6.55 (d, 1H).

REFERENCE EXAMPLE 16

4-Bromo-2-(5-methoxy-1-carboxylic acid tert-butyl ester-1H-indol-3-yl)-1-(toluene-4-sulfonyl)-1H-pyrrolo[2,3-b]pyridine

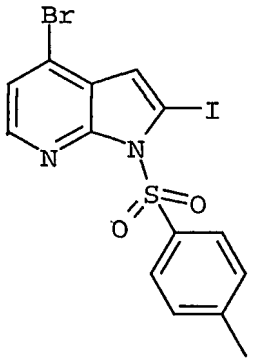


A microwave tube (Smith process vial, 2-5ml) was charged with 4-bromo-2-iodo-1-(toluene-4-sulfonyl)-1H-pyrrolo[2,3-b]pyridine (100mg, Reference Example 17) boronic acid (61mg), saturated aqueous sodium hydrogenocarbonate (1ml), $Pd(PPh_3)_4$ (20mg) and dimethylformamide (4 ml) . The tube was capped and the resulting mixture was heated at 60°C in a microwave oven for 30 minutes. Water (10ml) was added and the reaction mixture was extracted with ethyl acetate (10ml). The organic layer was washed with water, then with brine, then dried over magnesium sulfate and then concentrated under vacuum. The residue was subjected to column chromatography on silica eluting with a mixture of

ethyl acetate and heptane (15:85, v/v) to give 4-bromo-2-(5-methoxy-1-carboxylic acid tert-butyl ester-1H-indol-3-yl)-1-(toluene-4-sulfonyl)-1H-pyrrolo[2,3-b]pyridine (30mg) as a cream solid. MS: 598 (MH^+). HPLC: R_T = 7.82 minutes.

REFERENCE EXAMPLE 17

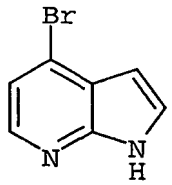
4-Bromo-2-iodo-1-(toluene-4-sulfonyl)-1H-pyrrolo[2,3-b]pyridine



A solution of 4-bromo-1-(toluene-4-sulfonyl)-1H-pyrrolo[2,3-b]pyridine [930mg, Reference Example 13(b)] in tetrahydrofuran (5ml) was cooled to –70°C then treated with lithium diisopropylamide (1.45ml of a 2M solution in tetrahydrofuran). The mixture was stirred at –70°C for 1 hour, then treated with a solution of iodine (1.01g) in tetrahydrofuran (7ml) whilst maintaining the temperature below -60°C. The reaction mixture was stirred and allowed to warm to room temperature over 3 hours then diluted with saturated aqueous ammonium chloride solution (50ml) and then extracted three times with ethyl acetate (100ml). The combined organics were washed with brine (50ml), then dried over sodium sulfate and then evaporated under vacuum. The residue was subjected to column chromatography on silica eluting with a mixture of heptane and ethyl acetate (9:1, v/v) to give 4-bromo-2-iodo-1-(toluene-4-sulfonyl)-1H-pyrrolo[2,3-b]pyridine (1.06g) as a white solid. MS: 479(MH^+). ^{1}HNMR ($CDCl_3$): δ 8.45 (d, 1H), 8.1 (d,2H), 7.60 (d, 1H), 7.26 (d, 2H), 7.19 (s, 1H), 2.37(s, 3H).

REFERENCE EXAMPLE 18

4-Bromo-1H-pyrrolo[2,3-b]pyridine

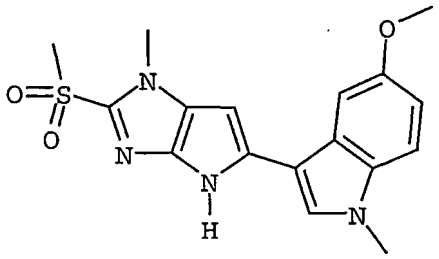


A mixture of 1H-pyrrolo[2,3-b]pyridine-7-oxide (1g, Reference Example 15) and phosphorus oxybromide(10.7g) was stirred at 45°C for 18 hours then 24 hours at 50°C. The reaction mixture was cooled to ambient temperature then treated with phosphorus oxybromide (10.7g). The reaction mixture

was then stirred at 50°C for 5 hours. The reaction mixture was carefully treated with water (10ml) then reheated to 80-90°C for 1 hour. The reaction mixture was cooled to room temperature then neutralized to pH=8-9 with 5N potassium hydroxide and then extracted three times with ethyl acetate (50ml). The combined organics were washed with brine (50ml), then dried over sodium sulfate and then evaporated under vacuum. The residue was subjected to column chromatography using a mixture of ethyl acetate and heptane (20:80, v/v) to give 4-bromo-1H-pyrrolo[2,3-b]pyridine (850mg)as a white solid. MS: 198(MH^+). HPLC: R_T = 3.23 minutes.

REFERENCE EXAMPLE 19

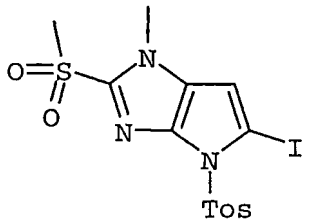
5-(5-methoxy-1-methyl-1H-indol-3-yl)-1-methyl-2-methylsulfonyl-1H-pyrrolo[2,3-d]imidazole



is prepared by coupling 5-iodo-1-methyl-2-methylsulfonyl-4-(toluene-4-sulfonyl)-1H-pyrrolo[2,3-d]imidazole (Reference Example 20) with 1-tert-butyloxycarbonyl-5-methoxy-1H-indole-3-boronic acid in the presence of tetrakis(triphenylphosphine)palladium(0) and sodium bicarbonate, in aqueous dimethylformamide at about reflux temperature.

REFERENCE EXAMPLE 20

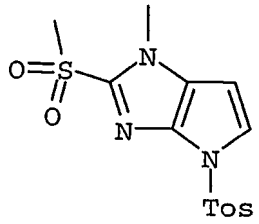
5-Iodo-1-methyl-2-methylsulfonyl-4-(toluene-4-sulfonyl)-1H-pyrrolo[2,3-d]imidazole



By proceeding in a manner similar to Reference Example 17 above but using 1-methyl-2-methylsulfonyl-4-(toluene-4-sulfonyl)-1H-pyrrolo[2,3-d]imidazole (Reference Example 21) there was prepared 5-iodo-1-methyl-2-methylsulfonyl-4-(toluene-4-sulfonyl)-1H-pyrrolo[2,3-d]imidazole as a beige solid. MS: 479(MH+). HPLC: RT = 5.27 minutes.

REFERENCE EXAMPLE 21

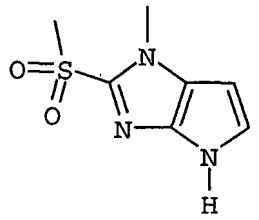
1-Methyl-2-methylsulfonyl-4-(toluene-4-sulfonyl)-1H-pyrrolo[2,3-d]imidazole



A mixture of 2-methylsulfonyl-1-methylpyrrolo[2,3-d]imidazole (0.704mmol, Reference Example 22), p-toluene sulfonyl chloride (148mg), aqueous sodium hydroxide (534mg in 1.7ml of water) and tetrabutylammonium sulfate (5 mg) in toluene (350ml) was stirred at room temperature for 12 hours. The reaction mixture was diluted with water (20ml) and extracted three times with ethyl acetate (15ml). The combined organics were washed with brine (20ml), dried over sodium sulfate, filtered and evaporated under vacuum. The residue was subjected to column chromatography using on silica eluting with a mixture of heptane and ethyl acetate (1:1, v/v) to give 1-methyl-2-methylsulfonyl-4-(toluene-4-sulfonyl)-1H-pyrrolo[2,3-d]imidazole (173 mg) as an orange oil. MS: 354(MH^+).

REFERENCE EXAMPLE 22

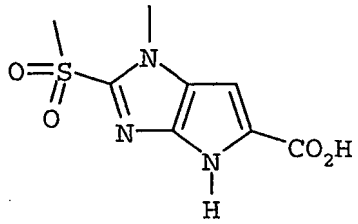
2-Methylsulfonyl-1-methylpyrrolo[2,3-d]imidazole



A microwave tube (Smith process vial, 2-5ml) was charged with 2-methylsulfonyl-1-methylpyrrolo[2,3-d]imidazole-5- carboxylic acid (70mg, Reference Example 23), copper (37mg) and quinoline (1.5ml) . The tube was capped and the resulting mixture was heated at 250°C in a microwave oven for 30 minutes. Water (10ml) was added and the reaction mixture was extracted with ethyl acetate (10ml). The organic layer was washed with water, brine, dried over magnesium sulfate and concentrated under vacuum to give 2-methylsulfonyl-1-methylpyrrolo[2,3-d]imidazole which was used without further purification. MS: 200.1(MH^+). HPLC: R_T = 2.28 minutes.

REFERENCE EXAMPLE 23

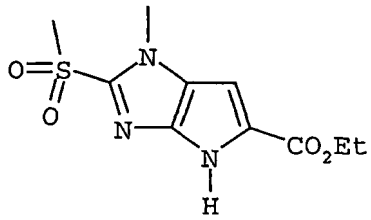
2-Methylsulfonyl-1-methylpyrrolo[2,3-d]imidazole-5-carboxylic acid



A mixture of ethyl 2-methylsulfonyl-1-methylpyrrolo[2,3-d]imidazole-5- carboxylate (130mg) and potassium hydroxide (30mg, Reference Example 24) in methanol (3ml) was refluxed for 1 hour. After cooling to room temperature and evaporation of the methanol, the residue was dissolved in the minimum amount of water, filtered and the mother liquor acidified to pH=1 with aqueous hydrochloric acid (5%). The resulting precipitate was filtered, then washed with water (10ml) and then dried under vacuum to give 2-methylsulfonyl-1-methylpyrrolo[2,3-d]imidazole-5-carboxylic acid (95mg)as a white solid. MS: 244(MH^+). HPLC: R_T = 2.5 minutes.

REFERENCE EXAMPLE 24

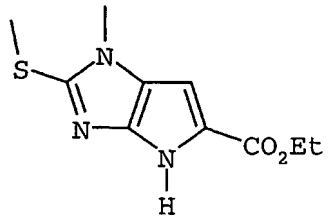
Ethyl 2-methylsulfonyl-1-methyl-pyrrolo[2,3-d]imidazole-5- carboxylate



To a stirring solution of ethyl 2-methylthio-1-methyl-pyrrolo[2,3-d]imidazole-5-carboxylate (1.09 mmol, Reference example 25) in methylene chloride (30ml) at 0°C was added sodium bicarbonate (1.06g), followed by m-chloroperbenzoic acid (1.06g). The reaction mixture was stirred at 0 C for 2 hours, then at room temperature for 12 hours. The mixture was poured into water (30ml) and extracted three times with methylene chloride (20ml). The organic layer was washed with brine (30ml), then dried over magnesium sulfate and then evaporated to give ethyl 2-methylsulfonyl-1-methyl-pyrrolo[2,3-d]imidazole-5- carboxylate as a yellow solid. MS: 272 (MH^+).

REFERENCE EXAMPLE 25

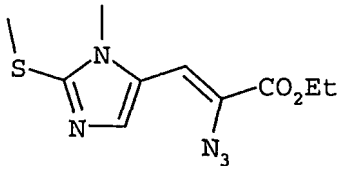
Ethyl 2-methylthio-1-methyl-pyrrolo[2,3-d]imidazole-5-carboxylate



A solution of ethyl α-azido-β-(2-methylthio-1-imidazol-5-yl)acrylate (3g, Reference Example 26) in toluene (30ml) was refluxed for 14 hours. The solvent was evaporated. The residue was subjected to column chromatography using ethyl acetate as eluent to give ethyl 2-methylthio-1-methyl-pyrrolo[2,3-d]imidazole-5-carboxylate as an orange solid. MS: 240(MH^+).

REFERENCE EXAMPLE 26

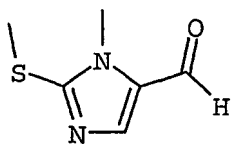
Ethyl α-azido-β-(2-methylthio-1-imidazol-5-yl)acrylate



To a stirring solution of sodium (1.22g) in absolute ethanol (45ml) at -30°C was added a solution of ethyl azidoacetate (6.8g) and 2-methylthio-5-formyl-1-methylimidazole (2.75g, Reference Example 27) in a mixture of absolute ethanol (28ml) and tetrahydrofurane (28ml) keeping the temperature below -20°C. After 2 hours at –10°C, the mixture was added to a saturated solution of ammonium chloride (100ml). The mixture was extracted three times with diethylether (50ml). The combined organics were washed with brine (50ml), then dried over sodium sulfate and then evaporated. The residue was subjected to column chromatography on silica eluting with a mixture of ethyl acetate and heptane (1/1, v/v) to give ethyl α-azido-β-(2-methylthio-1-imidazol-5-yl)acrylate as a yellow solid (2.5g). MS: 268 (MH^+). HPLC: R_T = 3.13 minutes.

REFERENCE EXAMPLE 27

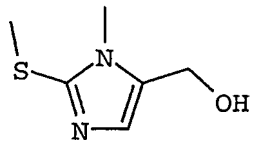
2-Methylthio-5-formyl-1-methylimidazole



Manganese dioxide (59g) was added to a solution of 5-(hydroxymethyl)-2-methylthio-1-methylimidazole (16.2g, Reference Example 28) in dichloromethane (360ml). The reaction mixture was stirred at 50°C for 12 hours. The suspension was filtered through a pad of Celite. The filtrate was evaporated to give 2-methylthio-5-formyl-1-methylimidazole (15.1g) as a yellow solid. MS: 157(MH^+). HPLC: R_T =1.55 minutes.

REFERENCE EXAMPLE 28

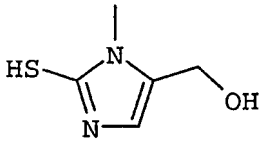
5-(Hydroxymethyl)-2-methylthio-1-methylimidazole



A solution of 5-(hydroxymethyl) -2-mercapto-1-methylimidazole (5g, Reference Example 29) in methanol (500ml) was added dropwise to aqueous sodium hydroxide (36ml, 1N) at room temperature. The yellow suspension is stirred for 10 minutes then treated dropwise with iodomethane (2.3ml) and stirring was continued for 18 hours. The reaction mixyture was evaporated and the residue was dissolved in water (100ml). This solution was extracted three times with dichloromethane (50ml). The combined extracts were evaporated and the residue was recrystallized from diethylether to give 5-(hydroxymethyl)-2-methylthio-1-methylimidazole (4.8g) as a beige solid. MS: 159(MH^+). ^{1}HNMR ($CDCl_3$): δ 6.8 (s, 1H), 5.1 (t, 1H), 4.4 (d, 2H), 3.55 (s, 3H), 2.45 (s, 3H).

REFERENCE EXAMPLE 29

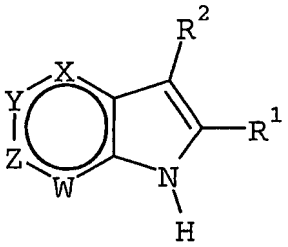
5-(Hydroxymethyl) -2-mercapto-1-methylimidazole



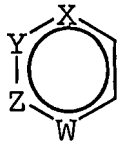
A mixture of dihydroxyacetone dimer (128g), potassium thiocyanate (207g) and methylamine hydrochloride (124g) was added to a mixture of acetic acid (160ml) and 1-butanol (1000ml). The resulting suspension was stirred for 72 hours after which it was suspended in 200 ml of water and filtered. The filter cake was washed with water (500ml) and then diethyl ether (500ml). The beige solid was dried in vacuo to give 5-(hydroxymethyl) -2-mercapto-1-methylimidazole (126 g). MS:145 [MH^+].

WHAT IS CLAIMED IS:

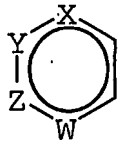
1. A process for preparing a compound of the formula



wherein

 is a six membered aromatic ring in which X represents N or C-R^{10}, Y and Z are each

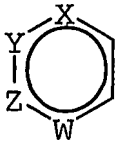
independently selected from CH and CR^3 and W is N; or

 is a six membered aromatic ring in which X represents C-R^{10}, Y and W are both N and Z

is CR^3; or

 is a six membered aromatic ring in which Y represents CR^3, Z and W are both N, and X is

N or CR^{10}; or

 is a five membered aromatic ring in which

(a) Y represents a direct bond, W is N, Z is CR^{12} and X is O, S or NR^{11}, or

(b) Y represents a direct bond, W is N, X is CR^{10} and Z is O, S, or NR^{13}, or

(c) Y represents a direct bond, W is O, X is CR^{10} and Z is N or CR^{12}, or

(d) Y represents a direct bond, W is O, X is N and Z is CR^{12};

R^1 represents aryl or heteroaryl, each optionally substituted by one or more groups selected from alkylenedioxy, alkenyl, alkenyloxy, alkynyl, aryl, cyano, halo, hydroxy, heteroaryl, heterocycloalkyl,

nitro, R^4, -C(=O)-R^9, -C(=O)-OR^5, -C(=O)-NY^1Y^2, -C(=O)-NSO_2-R^7, -NY^1Y^2, -N(R^6)-C(=O)-R^7, -N(R^6)-C(=O)-NY^3Y^4, -N(R^6)-C(=O)-OR^7, -N(R^6)-SO_2-R^7, -N(R^6)-SO_2-NY^3Y^4, -SO_2-NY^1Y^2, SO_2-NY^1C(=O)-R^7, and -Z^1R^9;

R^2 represents hydrogen, acyl, cyano, halo, lower alkenyl, -Z^1R^4, -SO_2NY^3Y^4, -NY^1Y^2 or lower alkyl optionally substituted by a substituent selected from cyano, heteroaryl, heterocycloalkyl, hydroxy, -Z^1R^4, -C(=O)-NY^1Y^2, -CO_2R^8, -NY^3Y^4, -N(R^6)-C(=O)-R^9, -N(R^6)-C(=O)-NY^1Y^2, -N(R^6)-C(=O)-OR^7, -N(R^6)-SO_2-R^7, -N(R^6)-SO_2-NY^3Y^4, -SO_2NY^1Y^2 and one or more halogen atoms;

R^3 represents hydrogen, aryl, cyano, halo, heteroaryl, -Z^1R^4, -C(=O)-OR^5, -C(=O)-NY^1Y^2 or lower alkyl optionally substituted with hydroxy or NY^5Y^6;

R^4 represents alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl or heterocycloalkylalkyl, each optionally substituted by one or more groups selected from aryl, cycloalkyl, cyano, halo, heteroaryl, heterocycloalkyl, hydroxy, -CHO or a 5-, 6- or 7-membered cyclic acetal derivative of such -CHO, -C(=O)-NY^1Y^2, -C(=O)-OR^5, -NY^1Y^2, -N(R^6)-C(=O)-R^7, -N(R^6)-C(=O)-NY^3Y^4, -N(R^6)-SO_2-R^7, -N(R^6)-SO_2-NY^3Y^4, and -Z^1R^7;

R^5 represents hydrogen, alkyl, alkenyl, aryl, arylalkyl, heteroaryl or heteroarylalkyl;

R^6 represents hydrogen or lower alkyl;

R^7 represents alkyl, aryl, arylalkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl or heterocycloalkylalkyl;

R^8 represents hydrogen or lower alkyl;

R^9 represents aryl or heteroaryl; or alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl or heterocycloalkylalkyl, each optionally substituted by one or more substituents selected from aryl, cycloalkyl, cyano, halo, heteroaryl, heterocycloalkyl, hydroxy -CHO or a 5-, 6- or 7-membered cyclic acetal derivative of such -CHO, -C(=O)-NY^1Y^2, -C(=O)-OR^5, -NY^1Y^2, -N(R^6)-C(=O)-R^7, -N(R^6)-C(=O)-NY^3Y^4, -N(R^6)-SO_2-R^7, -N(R^6)-SO_2-NY^3Y^4 and -Z^1R^7;

R^{10} represents H, halo, cyano, hydroxy, nitro, R^4, -NY^1Y^2, -Z^1R^4, -C(=O)-OR^5, -C(=O)-R^9, -C(=O)-NY^1Y^2, -N(R^8)-C(=O)-R^4, -N(R^8)-C(=O)-NY^1Y^2, -N(R^8)-C(=O)-OR^5, -SO_2-NY^3Y^4 or -N(R^8)-SO_2-R^9, or R^{10} may be aryl, heteroaryl, alkenyl or alkynyl, each optionally substituted by one or more groups selected from aryl, cyano, halo, hydroxy, heteroaryl, heterocycloalkyl, nitro, -C(=O)-NY^1Y^2, -C(=O)-OR^5, –C(=O)NSO_2-R^7, -NY^1Y^2, -N(R^6)-C(=O)-R^7, -N(R^6)-C(=O)-NY^3Y^4,

$-N(R^6)-C(=O)-OR^7$, $-N(R^6)-SO_2-R^7$, $-N(R^6)-SO_2-NY^3Y^4$, $-SO_2-NY^1Y^2$, $-SO_2-NY^1C(=O)-R^7$ and $-Z^1R^9$;

R^{11} represents H, CN, R^4, $-C(=O)-OR^5$, $-C(=O)-NY^1Y^2$, $-C(=O)-R^9$, $-SO_2-NY^3Y^4$, $-SO_2-R^7$, or aryl, heteroaryl, alkenyl or alkynyl, each optionally substituted by one or more groups selected from aryl, cyano, halo, hydroxy, heteroaryl, heterocycloalkyl, nitro,$-C(=O)-NY^1Y^2$, $-C(=O)-OR^5$, $-NY^1Y^2$, $-N(R^6)-C(=O)-R^7$, $-N(R^6)-C(=O)-NY^3Y^4$, $-N(R^6)-C(=O)-OR^7$, $-N(R^6)-SO_2-R^7$, $-N(R^6)-SO_2-NY^3Y^4$, $-SO_2-NY^1Y^2$ and $-Z^1R^4$;

R^{12} represents cyano, H, $-NY^5Y^6$, $-OR^6$, $-SO_2Me$ or lower alkyl optionally substituted with hydroxy or $-NY^5Y^6$;

R^{13} represents H, lower alkyl optionally substituted with hydroxy or NY^5Y^6;

Y^1 and Y^2 are independently hydrogen, alkenyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, or alkyl optionally substituted by one or more groups selected from aryl, halo, heteroaryl, hydroxy, $-C(=O)-NY^3Y^4$, $-C(=O)-OR^5$, $-NY^3Y^4$, $-N(R^6)-C(=O)-R^7$, $-N(R^6)-C(=O)-NY^3Y^4$, $-N(R^6)-SO_2-R^7$, $-N(R^6)-SO_2-NY^3Y^4$ and $-OR^7$; or the group $-NY^1Y^2$ may form a cyclic amine;

Y^3 and Y^4 are independently hydrogen, alkenyl, alkyl, aryl, arylalkyl, cycloalkyl, heteroaryl or heteroarylalkyl; or the group $-NY^3Y^4$ may form a cyclic amine;

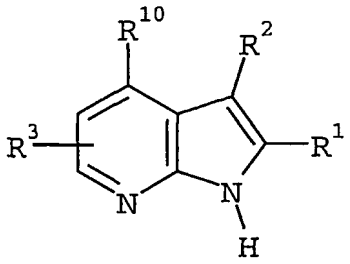
Y^5 and Y^6 are independently hydrogen or lower alkyl;

Z^1 represents O or $S(O)_n$; and

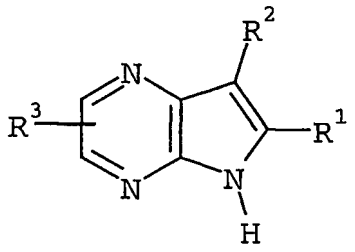
n is zero or an integer 1 or 2;

comprising at least one step employing microwave energy.

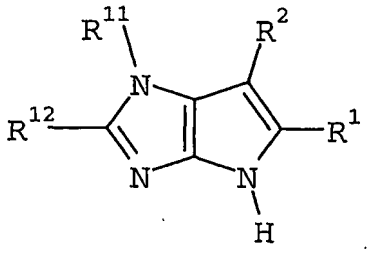
2. A process according to claim 1 for preparing a compound of the formula



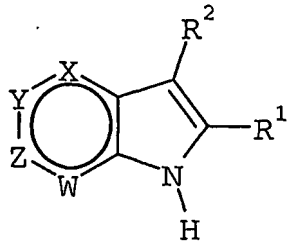
3. A process according to claim 1 for preparing a compound of the formula



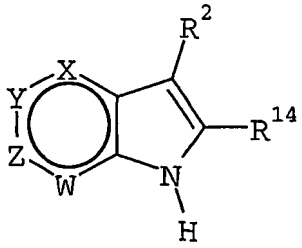
4. A process according to claim 1 for preparing a compound of the formula



5. A process according to claim 1 for preparing a compound of the formula

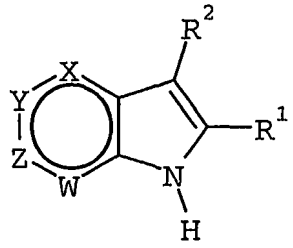


wherein R^1 is aryl substituted by $-NY^1Y^2$ or wherein R^1 is heteroaryl substituted by $-NY^1Y^2$ comprising reacting a compound of the formula

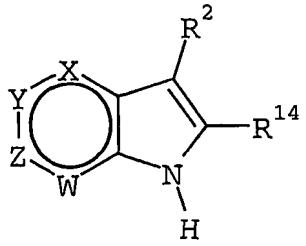


wherein R^{14} is aryl substituted by $-OSO_2CH_3$ or heteroaryl substituted by $-OSO_2CH_3$ with an amine of formula HNY^1Y^2, in the presence of an inert solvent, at a temperature of about 200°C, wherein the temperature is maintained by employing microwave energy.

6. A process according to claim 1 for preparing a compound of the formula

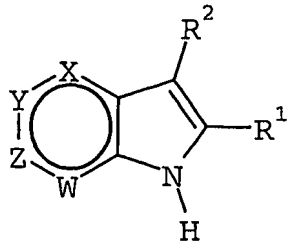


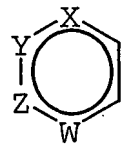
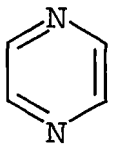
wherein R^1 is aryl substituted by $-NY^1Y^2$ or wherein R^1 is heteroaryl substituted by $-NY^1Y^2$ comprising reacting a compound of the formula

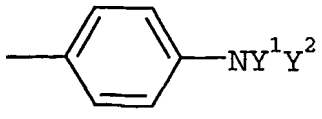


wherein R^{14} is aryl substituted by $-OSO_2CF_3$ or heteroaryl substituted by $-OSO_2CF_3$ with an amine of formula HNY^1Y^2, in the presence of an inert solvent, at a temperature of about 200°C, wherein the temperature is maintained by employing microwave energy.

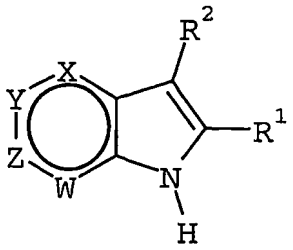
7. A process according to claim 5 or claim 6 for preparing a compound of the formula



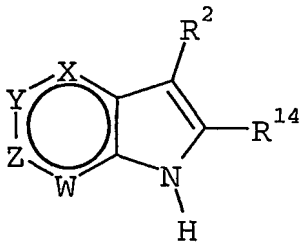
wherein  is  and R^1 is



8. A process according to claim 1 for preparing a compound of the formula



wherein R^1 is aryl substituted by $-NY^1Y^2$ or wherein R^1 is heteroaryl substituted by $-NY^1Y^2$ comprising reacting a compound of the formula



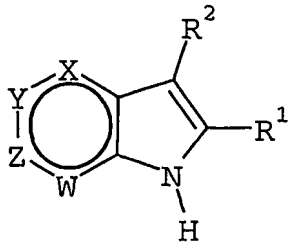
wherein R^{14} is aryl substituted by halo or heteroaryl substituted by halo with an amine of formula HNY^1Y^2, in the presence of an inert solvent, and in the presence of copper (I) iodide and sodium carbonate, at a temperature of about 200°C, wherein the temperature is maintained by employing microwave energy.

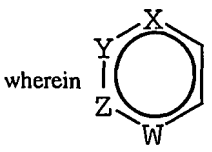
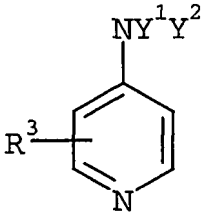
9. A process according to any one of claims 5, 6 or 7 wherein the inert solvent is dimethylformamide or dioxane.

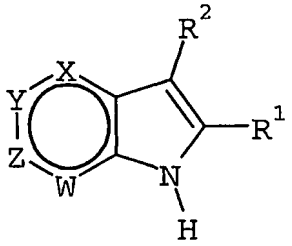
10. A process according to claim 8 wherein the inert solvent is dimethylformamide.

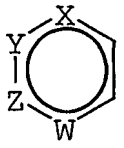
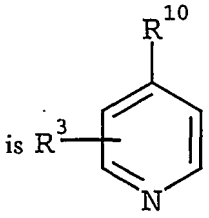
11. A process according to claim 8 wherein halo is bromo or iodo.

12. A process according to claim 1 for preparing a compound of the formula



wherein  is  comprising reacting a compound of the formula



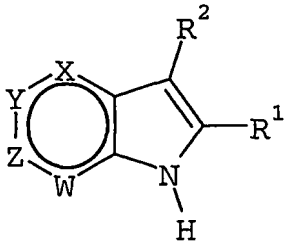
wherein  is 

and R^{10} is halo, with an amine of the formula HNY^1NY^2, in the presence of an inert solvent, at a temperature of about 210°C, wherein the temperature is maintained by employing microwave energy.

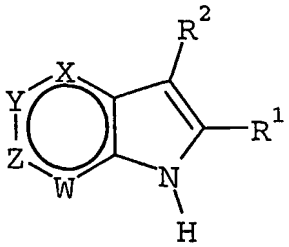
13. A process according to claim 12 wherein the inert solvent is α,α,α-trifluorotoluene.

14. A process according to claim 12 wherein halo is bromo or iodo.

15. A process according to claim 1 for preparing a compound of the formula



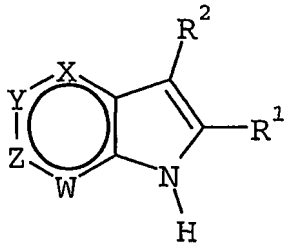
wherein R^1 is aryl substituted by aryl, or R^1 is heteroaryl substituted by aryl, comprising reacting a compound of the formula



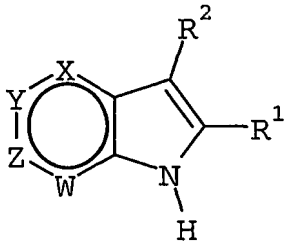
wherein R^1 is aryl substituted by halo, or R^1 is heteroaryl substituted by halo, with an aryl-boronic acid, in the presence of tetrakis(triphenylphosphine)palladium (0) and aqueous sodium carbonate, in the

presence of an inert solvent, at a temperature of about 180°C, wherein the temperature is maintained by employing microwave energy.

16. A process according to claim 1 for preparing a compound of the formula



wherein R^1 is aryl substituted by heteroaryl, or R^1 is heteroaryl substituted by heteroaryl, comprising reacting a compound of the formula

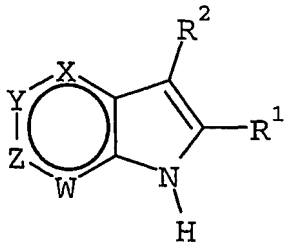


wherein R^1 is aryl substituted by halo, or R^1 is heteroaryl substituted by halo, with a heteroaryl-boronic acid, in the presence of tetrakis(triphenylphosphine)palladium (0) and aqueous sodium carbonate, in the presence of an inert solvent, at a temperature of about 180°C, wherein the temperature is maintained by employing microwave energy.

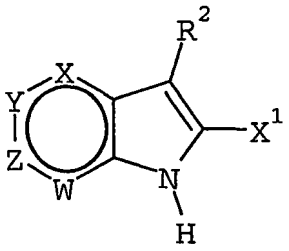
17. A process according to claim 15 or claim 16 wherein the inert solvent is dioxane.

18. A process according to claim 15 or 16 wherein halo is bromo or iodo.

19. A process according to claim 1 for preparing a compound of the formula

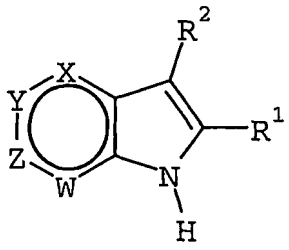


wherein R^1 is aryl substituted by aryl, or R^1 is heteroaryl substituted by aryl, comprising reacting a compound of the formula

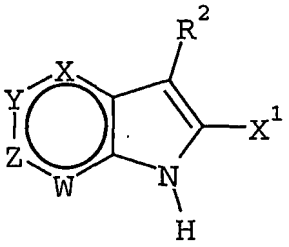


wherein X^1 is iodo, with an aryl-boronic acid, in the presence of tetrakis(triphenylphosphine)palladium (0) and aqueous sodium carbonate, in the presence of an inert solvent, at a temperature of about 60°C, wherein the temperature is maintained by employing microwave energy.

20. A process according to claim 1 for preparing a compound of the formula



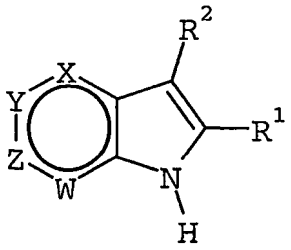
wherein R^1 is aryl substituted by heteroaryl, or R^1 is heteroaryl substituted by heteroaryl, comprising reacting a compound of the formula



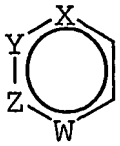
wherein X^1 is iodo, with a heteroaryl-boronic acid, in the presence of tetrakis(triphenylphosphine)palladium (0) and aqueous sodium carbonate, in the presence of an inert solvent, at a temperature of about 60°C, wherein the temperature is maintained by employing microwave energy.

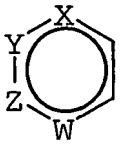
21. A process according to claim 19 or claim 20 wherein the inert solvent is dimethylformamide.

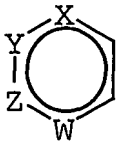
22. A step in a process for preparing a compound of the formula



wherein

 is a six membered aromatic ring in which X represents N or C-R^{10}, Y and Z are each independently selected from CH and CR^3 and W is N; or

 is a six membered aromatic ring in which X represents C-R^{10}, Y and W are both N and Z is CR^3; or

 is a six membered aromatic ring in which Y represents CR^3, Z and W are both N, and X is N or CR^{10}; or

 is a five membered aromatic ring in which

(a) Y represents a direct bond, W is N, Z is CR^{12} and X is O, S or NR^{11}, or

(b) Y represents a direct bond, W is N, X is CR^{10} and Z is O, S, or NR^{13}, or

(c) Y represents a direct bond, W is O, X is CR^{10} and Z is N or CR^{12}, or

(d) Y represents a direct bond, W is O, X is N and Z is CR^{12};

R^1 represents aryl or heteroaryl, each optionally substituted by one or more groups selected from alkylenedioxy, alkenyl, alkenyloxy, alkynyl, aryl, cyano, halo, hydroxy, heteroaryl, heterocycloalkyl, nitro, R^4, -C(=O)-R^9, -C(=O)-OR^5, -C(=O)-NY^1Y^2, -C(=O)-NSO_2-R^7, -NY^1Y^2, -N(R^6)-C(=O)-R^7, -N(R^6)-C(=O)-NY^3Y^4, -N(R^6)-C(=O)-OR^7, -N(R^6)-SO_2-R^7, -N(R^6)-SO_2-NY^3Y^4, -SO_2-NY^1Y^2, SO_2-NY^1C(=O)-R^7, and -Z^1R^9;

R^2 represents hydrogen, acyl, cyano, halo, lower alkenyl, $-Z^1R^4$, $-SO_2NY^3Y^4$, $-NY^1Y^2$ or lower alkyl optionally substituted by a substituent selected from cyano, heteroaryl, heterocycloalkyl, hydroxy, $-Z^1R^4$, $-C(=O)-NY^1Y^2$, $-CO_2R^8$, $-NY^3Y^4$, $-N(R^6)-C(=O)-R^9$, $-N(R^6)-C(=O)-NY^1Y^2$, $-N(R^6)-C(=O)-OR^7$, $-N(R^6)-SO_2-R^7$, $-N(R^6)-SO_2-NY^3Y^4$, $-SO_2NY^1Y^2$ and one or more halogen atoms;

R^3 represents hydrogen, aryl, cyano, halo, heteroaryl, $-Z^1R^4$, $-C(=O)-OR^5$, $-C(=O)-NY^1Y^2$ or lower alkyl optionally substituted with hydroxy or NY^5Y^6;

R^4 represents alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl or heterocycloalkylalkyl, each optionally substituted by one or more groups selected from aryl, cycloalkyl, cyano, halo, heteroaryl, heterocycloalkyl, hydroxy, -CHO or a 5-, 6- or 7-membered cyclic acetal derivative of such -CHO, $-C(=O)-NY^1Y^2$, $-C(=O)-OR^5$, $-NY^1Y^2$, $-N(R^6)-C(=O)-R^7$, $-N(R^6)-C(=O)-NY^3Y^4$, $-N(R^6)-SO_2-R^7$, $-N(R^6)-SO_2-NY^3Y^4$, and $-Z^1R^7$;

R^5 represents hydrogen, alkyl, alkenyl, aryl, arylalkyl, heteroaryl or heteroarylalkyl;

R^6 represents hydrogen or lower alkyl;

R^7 represents alkyl, aryl, arylalkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl or heterocycloalkylalkyl;

R^8 represents hydrogen or lower alkyl;

R^9 represents aryl or heteroaryl; or alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl or heterocycloalkylalkyl, each optionally substituted by one or more substituents selected from aryl, cycloalkyl, cyano, halo, heteroaryl, heterocycloalkyl, hydroxy -CHO or a 5-, 6- or 7-membered cyclic acetal derivative of such -CHO, $-C(=O)-NY^1Y^2$, $-C(=O)-OR^5$, $-NY^1Y^2$, $-N(R^6)-C(=O)-R^7$, $-N(R^6)-C(=O)-NY^3Y^4$, $-N(R^6)-SO_2-R^7$, $-N(R^6)-SO_2-NY^3Y^4$ and $-Z^1R^7$;

R^{10} represents H, halo, cyano, hydroxy, nitro, R^4, $-NY^1Y^2$, $-Z^1R^4$, $-C(=O)-OR^5$, $-C(=O)-R^9$, $-C(=O)-NY^1Y^2$, $-N(R^8)-C(=O)-R^4$, $-N(R^8)-C(=O)-NY^1Y^2$, $-N(R^8)-C(=O)-OR^5$, $-SO_2-NY^3Y^4$ or $-N(R^8)-SO_2-R^9$, or R^{10} may be aryl, heteroaryl, alkenyl or alkynyl, each optionally substituted by one or more groups selected from aryl, cyano, halo, hydroxy, heteroaryl, heterocycloalkyl, nitro, $-C(=O)-NY^1Y^2$, $-C(=O)-OR^5$, $-C(=O)NSO_2-R^7$, $-NY^1Y^2$, $-N(R^6)-C(=O)-R^7$, $-N(R^6)-C(=O)-NY^3Y^4$, $-N(R^6)-C(=O)-OR^7$, $-N(R^6)-SO_2-R^7$, $-N(R^6)-SO_2-NY^3Y^4$, $-SO_2-NY^1Y^2$, $-SO_2-NY^1C(=O)-R^7$ and $-Z^1R^9$;

R^{11} represents H, CN, R^4, $-C(=O)-OR^5$, $-C(=O)-NY^1Y^2$, $-C(=O)-R^9$, $-SO_2-NY^3Y^4$, $-SO_2-R^7$, or aryl, heteroaryl, alkenyl or alkynyl, each optionally substituted by one or more groups selected from aryl,

cyano, halo, hydroxy, heteroaryl, heterocycloalkyl, nitro,-C(=O)-NY^1Y^2, -C(=O)-OR^5, -NY^1Y^2, -$N(R^6)$-C(=O)-R^7, -$N(R^6)$-C(=O)-NY^3Y^4, -$N(R^6)$-C(=O)-OR^7, -$N(R^6)$-SO_2-R^7, -$N(R^6)$-SO_2-NY^3Y^4, -SO_2-NY^1Y^2 and -Z^1R^4;

R^{12} represents cyano, H, -NY^5Y^6, -OR^6, –SO_2Me or lower alkyl optionally substituted with hydroxy or -NY^5Y^6;

R^{13} represents H, lower alkyl optionally substituted with hydroxy or NY^5Y^6;

Y^1 and Y^2 are independently hydrogen, alkenyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, or alkyl optionally substituted by one or more groups selected from aryl, halo, heteroaryl, hydroxy, -C(=O)-NY^3Y^4, -C(=O)-OR^5, -NY^3Y^4, -$N(R^6)$-C(=O)-R^7, -$N(R^6)$-C(=O)-NY^3Y^4, -$N(R^6)$-SO_2-R^7, -$N(R^6)$-SO_2-NY^3Y^4 and -OR^7; or the group -NY^1Y^2 may form a cyclic amine;

Y^3 and Y^4 are independently hydrogen, alkenyl, alkyl, aryl, arylalkyl, cycloalkyl, heteroaryl or heteroarylalkyl; or the group -NY^3Y^4 may form a cyclic amine;

Y^5 and Y^6 are independently hydrogen or lower alkyl;

Z^1 represents O or $S(O)_n$; and

n is zero or an integer 1 or 2;

comprising employing microwave energy.

INTERNATIONAL SEARCH REPORT

national Application No
PCT/US 02/20206

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D471/04 C07D487/04 B01J19/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D B01J

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,Y	WO 01 47922 A (DEPRETS STEPHANIE; LAI JUSTINE YEUN QUAI (GB); MORLEY ANDREW DAVID) 5 July 2001 (2001-07-05) Page 162, lines 7-21; page 165, lines 1-8.	1-22
Y	WO 99 51233 A (GOULET MARK T; MERCK & CO INC (US); WALSH THOMAS F (US); UJJAINWAL) 14 October 1999 (1999-10-14) Page 19, scheme E, and page 20, lines 9-32; page 40, step 1C.	1-22
Y	US 6 136 157 A (LARHED MATS ET AL) 24 October 2000 (2000-10-24) cited in the application Claims 1, 14; columns 11-12, table 2; column 16, lines 33-50.	1-22

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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'L' document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

'O' document referring to an oral disclosure, use, exhibition or other means

'P' document published prior to the international filing date but later than the priority date claimed

'T' later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

'X' document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

'Y' document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

'&' document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
17 September 2002	04/10/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Weisbrod, T

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

national Application No
PCT/US 02/20206

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
Y	LARHED, M. ET AL.: "Rapid Microwave.Assisted Suzuki Coupling on Solid-Phase" TETRAHEDRON LETT., vol. 37, no. 45, 1996, pages 8219-8222, XP002213778 the whole document	1-22
Y	LARHED. M; HALLBERG, A.: "Microwave-Promoted Palladium-Catalyzed Coupling Reactions" J. ORG. CHEM., vol. 61, 1996, pages 9582-9584, XP002213779 Table 1, entry 9.	1-22
Y	TRAXLER, P. M. ET AL.: "4-(Phenyl)pyrrolopyrimidines: Potent and Selective, ATP Site Directed Inhibitors of the EGF-Receptor Protein Tyrosine Kinase" J. MED. CHEM., vol. 39, no. 12, 1996, pages 2285-2292, XP002213780 Page 2287, scheme 1: 7d to 8d to 28.	1-22
Y	SALMORIA, G. V. ET AL.: "Aromatic Nucleophilic Substitution Under Microwave Irradiation" TETRAHEDRON LETT., vol. 39, 1998, pages 2471-2474, XP002213781 the whole document	1-22
Y	DATABASE CROSSFIRE BEILSTEIN 'Online! Beilstein Institut zur Foerderung der chemischen Wissenschaften, Frankfurt am Main, DE; XP002213782 Database Accession no. 5757295 (CNR): reaction 1. & TETRAHEDRON LETT., vol. 34, no. 16, 1993, pages 2673-2676,	1-22

INTERNATIONAL SEARCH REPORT

Information on patent family members

national Application No
PCT/US 02/20206

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		WO 0147922 A2	05-07-2001
WO 9951233 A	14-10-1999	AU 3210799 A	25-10-1999
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		JP 2002510630 T	09-04-2002
		WO 9951233 A1	14-10-1999
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US 6136157 A	24-10-2000	SE 509731 C2	01-03-1999
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		JP 2000510145 T	08-08-2000
		SE 9603913 A	14-01-1998
		WO 9743230 A1	20-11-1997